

# AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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VOLUME 60

JULY-DECEMBER, 1950

ST. LOUIS

THE C. V. MOSBY COMPANY

1950

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*Printed in the  
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*Press of  
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St. Louis*



# American Journal of Obstetrics and Gynecology

VOL. 60

JULY, 1950

No. 1

## Original Communications

### A STUDY OF ANTIDIURETIC EFFECT OF THE DEPRESSANT DRUGS USED IN ECLAMPSIA\*

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(From the Department of Obstetrics and Gynecology, State University of Iowa)

**E**CLAMPSIA today is still a major cause of maternal morbidity and mortality. We seem no closer to an understanding of its etiology than we were several decades ago. While the establishment of a uniform classification by the American Committee on Maternal Welfare<sup>1</sup> has done much to standardize our clinical study of the toxemias, it has done little to further our basic knowledge of this disorder.

Despite our lack of understanding of the etiology, the clinical management of these patients has greatly improved. Good prenatal care and the termination of pregnancy at the proper time have effectively reduced the morbidity and mortality from this disease.

The treatment of toxemia of pregnancy remains entirely empirical. Various investigators have attacked the several forms of this syndrome and focused their attention on a special symptom or manifestation. Methods for the control of salt and water metabolism have attracted attention and reasonably uniform schedules for the control of edema have been established. Depressant drugs have generally been employed to control the central nervous system irritability and to aid in lowering the elevated blood pressure in these patients.

Nearly all of the sedatives of our therapeutic armamentarium have been employed in the control of toxemic and eclamptic patients. Because of its universal availability, ease of administration, and reasonable effectiveness, morphine has become the most popular agent in the management of these patients.

\*Presented at the Sixtieth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 8 to 10, 1949.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

During the course of studies on sodium and water excretion of pregnant women,<sup>2</sup> it was observed that morphine reduced the flow of urine. It appeared possible that the oliguria of toxemia might be converted to anuria by heavy morphine sedation. Since a favorable prognosis is usually associated with a rising rate of urine secretion, it seemed desirable to study any possible reversal of this clinical response by morphine.

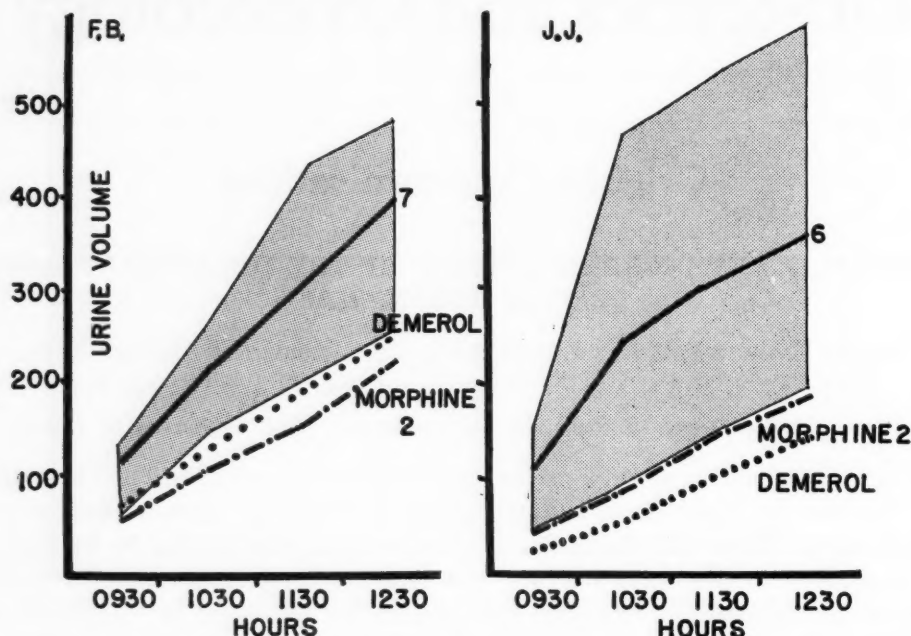


Fig. 1.—Oral fluids. For experimental procedure see text. Shaded area represents range of normal and the line through it is average of such observations. The right-hand numbers indicate the number of observations. Morphine and Demerol reduced urine volume below that of the lowest control day.

A review of the literature on renal physiology and the effect of the various sedatives used in toxemia and eclampsia appeared in previous publications from this laboratory.<sup>3</sup> The several mechanisms suggested to explain this antidiuretic effect of morphine (and other depressant drugs) may be summarized as follows: The urine volume may be reduced through the central or systemic depression of sleep, by a release of the pituitary antidiuretic hormone, or by a direct depression of renal physiology. Experiments were devised to study the diuretic-antidiuretic behavior of the various sedatives used in eclampsia and to explore the mechanism of their effect. This paper reports a series of studies conducted over several years to explore this problem.

### Experimental Procedures

#### *Morphine—Oral Fluids.*—

In the early experiments<sup>5</sup> a series of 14 pregnant women were fasted overnight and given a liquid breakfast of 1,000 c.c. at 7:00 A.M. The bladder was emptied by catheter at 8:30 A.M. and urine was collected at hourly intervals for four hours. On experimental days morphine\* or another depressant drug was

\*The dose of morphine employed in these experiments was 16 mg. (grain  $\frac{1}{4}$ ) given intravenously. The dose of the other sedatives was at a similar therapeutic level.

given parenterally at 9:00 A.M., the alternate day serving as control. Morphine and other narcotic drugs produced a significant antidiuretic response (Fig. 1).

### SUMMATION CURVES

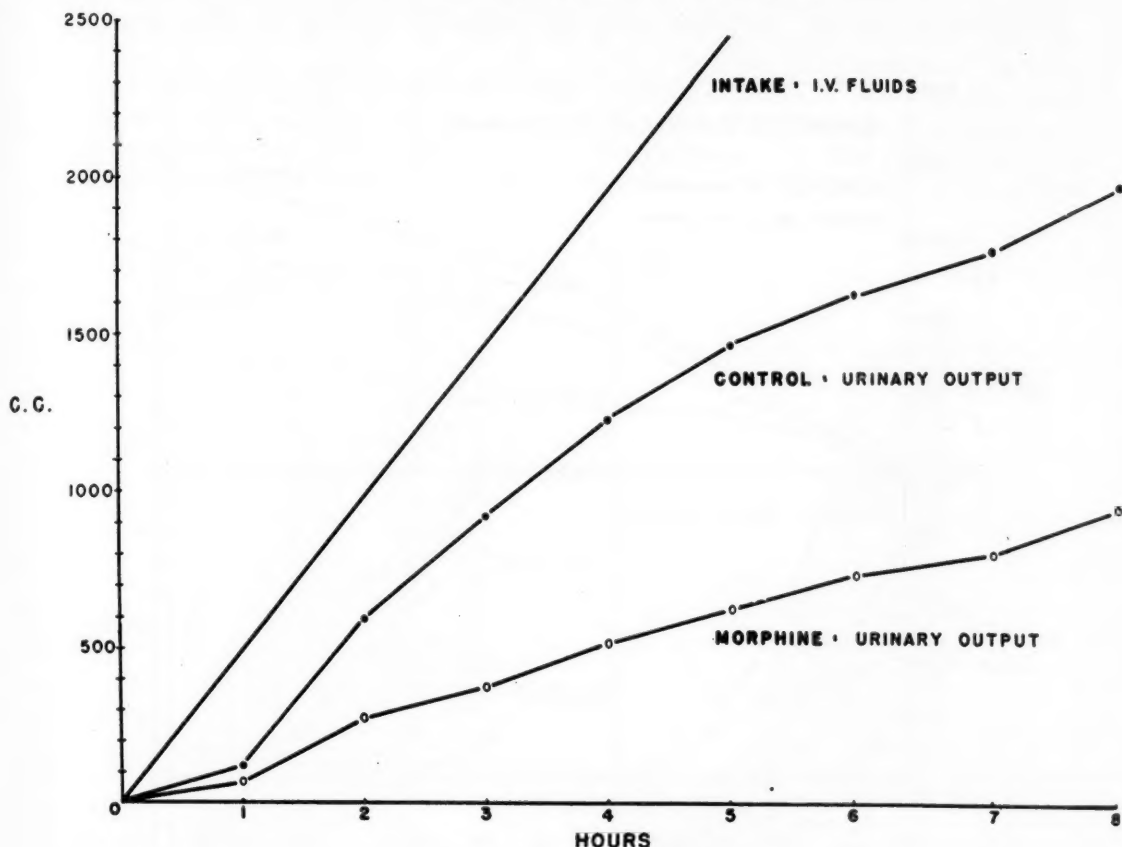


Fig. 2.—Parenteral fluids. See text for details of technique of experiment. Straight line indicates infusion of fluids and broken lines indicate urine volume. Morphine, 16 mg., significantly reduced urine volume. These curves represent an average of eleven subjects.

#### *Morphine—Parenteral Fluids.—*

Since it was possible that morphine interfered with the absorption of fluids from the gastrointestinal tract, experiments were planned to provide parenteral administration of fluids. Liquids were withheld after midnight and for the next sixteen hours. At 8:00 A.M. the bladder was emptied by an indwelling catheter and an intravenous infusion of 5 per cent dextrose was started and continued at a rate of approximately 400 c.c. per hour. Urine was collected at hourly intervals for a period of eight hours. On alternate days the subject was given 16 mg. of morphine (grain  $\frac{1}{4}$ ) intravenously at the onset of the infusion. Fifteen women (eleven pregnant and four nonpregnant) were studied under this schedule.<sup>6</sup>

The urine volume for the first three to six hours on the experimental day was significantly reduced; during the late afternoon and overnight period the urine volume of the experimental and control days approximated each other; it thus became apparent that morphine is an effective antidiuretic and that this effect is independent of gastrointestinal absorption (Figs. 2 and 3).

*Systemic Effect—Hypnotic Sleep.—*

In order to check the systemic effect of sedatives, the oral experiment was employed because of its simplicity. The first several experiments all showed some depression of the urine volume. There was no demonstrable change in the patient's respiration, pulse, or blood pressure which could account for the decreased urine volume. Hypnotic sleep was employed to study the effect of sleep

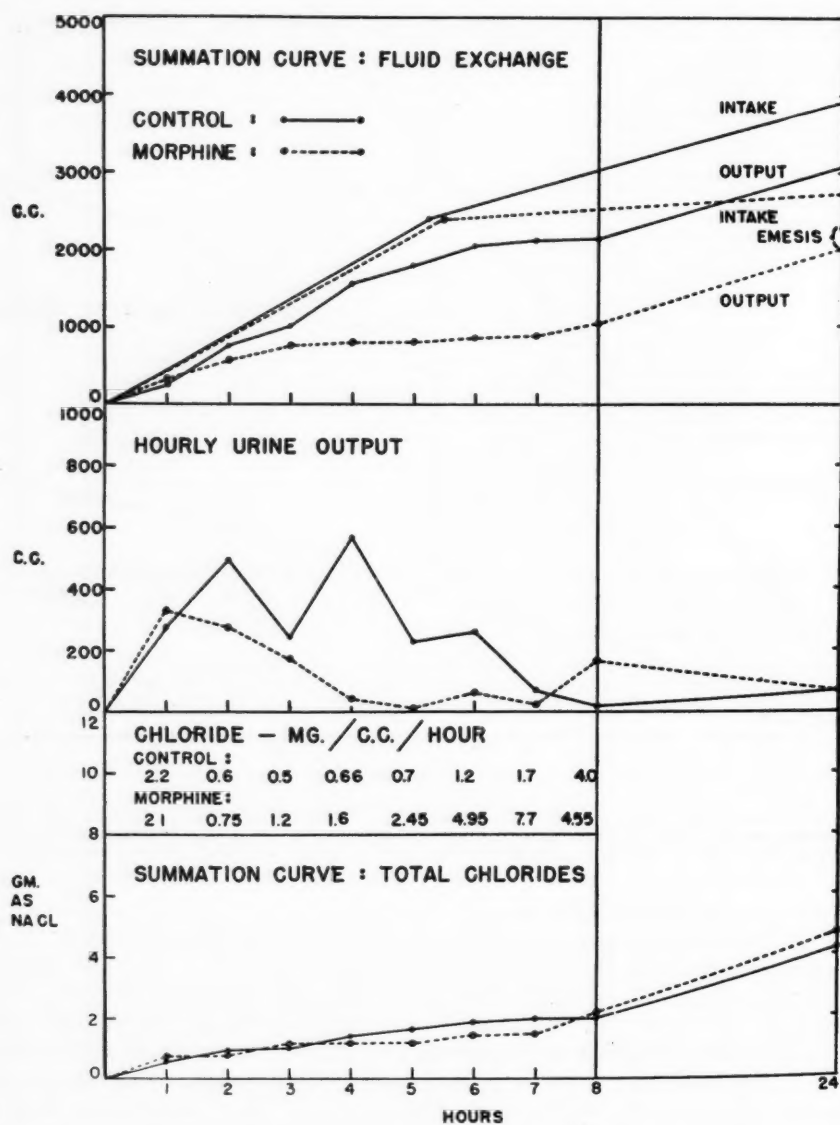


Fig. 3.—Composite diagram showing summation curves, hourly curves, and chloride excretion.

itself on renal function. At 9:00 A.M. on the experimental day, four subjects were hypnotized on three occasions by Dr. Wilbur Miller of the Department of Psychiatry. Hypnosis failed to alter the urine volume in these women (Figs. 4 and 5). Sleep induced by Avertin and paraldehyde likewise failed to reduce urine volume (Fig. 6).



The lack of systemic change under morphine and the lack of antidiuresis associated with hypnotic sleep and hypnotic drugs suggested that the urinary suppression of morphine was due to some mechanism other than the effect of sleep.

*The Role of the Pituitary.—*

De Bodo<sup>4</sup> and others have suggested that the antidiuretic effect of morphine is accomplished through the liberation of the antidiuretic hormone from the pituitary. Two patients with well-controlled diabetes insipidus were brought into the hospital for study. Pitressin administration was discontinued until the polydipsia and polyuria were re-established. The diagnosis was confirmed by the hypertonic saline test of Carter and Robbins.<sup>8</sup> At this point they were given intravenous fluids in the manner described above and morphine was added

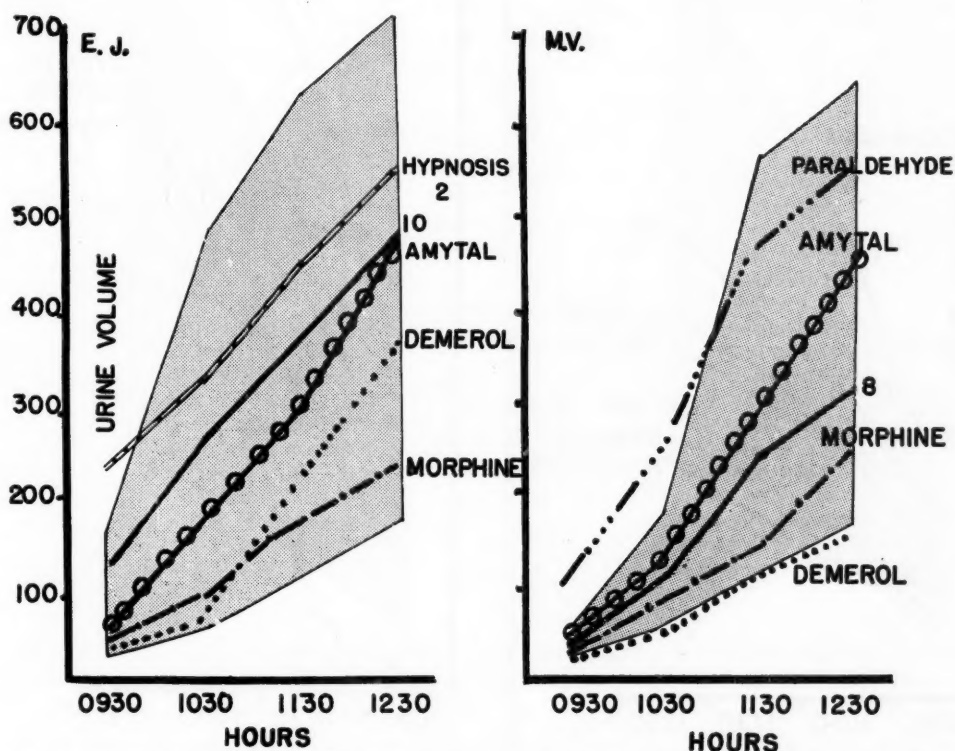


Fig. 4.—Oral fluids. For description of figure, see Fig. 1. Hypnosis and sleep induced by paraldehyde and Amytal did not depress urine volume.

on experimental days. In these subjects, as with normal pregnant women, morphine caused a significant reduction in urine volume, suggesting that at least in women morphine antidiuresis<sup>6</sup> appears to be independent of the pituitary (Figs. 2 and 7).

*Renal Clearances.—*

From these experiments it seemed probable that the antidiuretic effect of morphine and the other depressants was on the kidney itself rather than by some indirect extrarenal mechanism. In order to determine the mechanism of action within the kidney, recourse was made to renal clearances of sodium thio-sulphate and para-amino-hippurate which fractionate the kidney function into its tubular and glomerular components and provide and estimate of the total renal plasma flow.<sup>9</sup>

Experiments were conducted in the following manner. The patients were given 500 c.c. of fluids at bedtime, 1,000 c.c. of water at 7:00 A.M. and breakfast was omitted. At 8:00 A.M. an intravenous infusion containing appropriate amounts of the clearance agents was started and regulated by an electric pump to flow at the rate of 4 to 6 c.c. per minute. The bladder was emptied by an indwelling catheter. The patient was allowed to equilibrate for one hour and

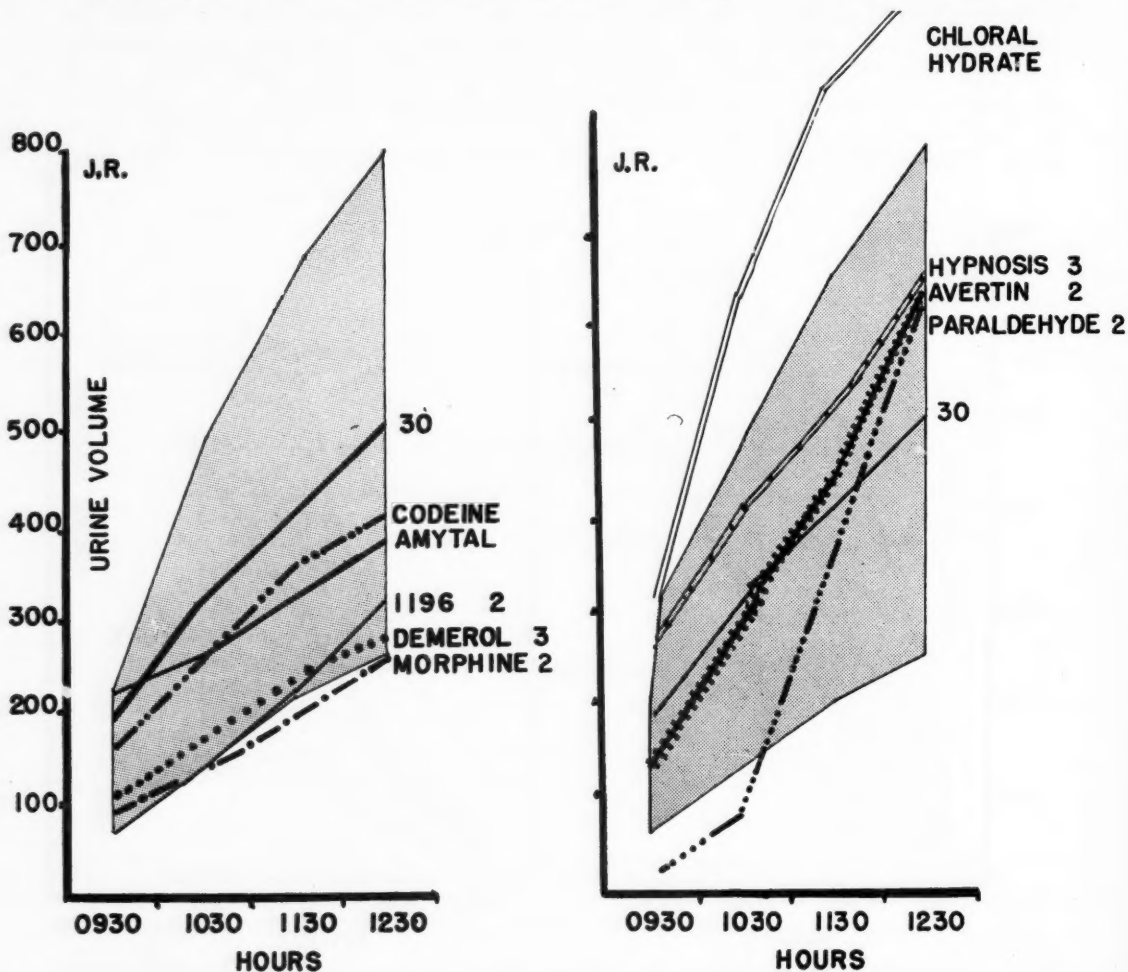


Fig. 5.—Oral fluids. This chart represents 47 observations on the same subject, 30 control and 17 experimental. The left chart groups the agents showing a reduction in urine volume

while the right chart shows those that did not affect urine volume or that tended to increase it. thereafter urine and blood samples were taken at fifteen minute intervals. After several such observations on experimental days, morphine (or other depressant) was given parenterally and a second set of observations was made. By chemical analysis of these two substances in the blood and urine it is possible to determine changes in renal plasma flow, glomerular filtration, filtration fraction, and reabsorption fraction.<sup>3</sup>

Morphine reduced the renal plasma flow and increased the reabsorption fraction in the fourteen subjects studied by this clearance technique (Fig. 8). These experiments suggest that the effect of morphine is on the vascular bed of the kidney and that the antidiuresis is produced by a decrease in plasma flow and filtration fraction, and an increase in the reabsorption fraction.

*Pitressin-Adrenalin Mechanism.*—

At this point in the studies it seemed wise to investigate the mechanism of action of the two hormones controlling urine volume, Adrenalin and Pitressin.<sup>3</sup> Using the clearance technique described above, ten subjects were studied after Adrenalin and ten after Pitressin administration. It was observed that Pitressin antidiuresis is effected largely by means of a greatly increased tubular reabsorption fraction as has been suggested by others. Renal plasma flow and glomerular filtration were not altered significantly (statistical analysis).

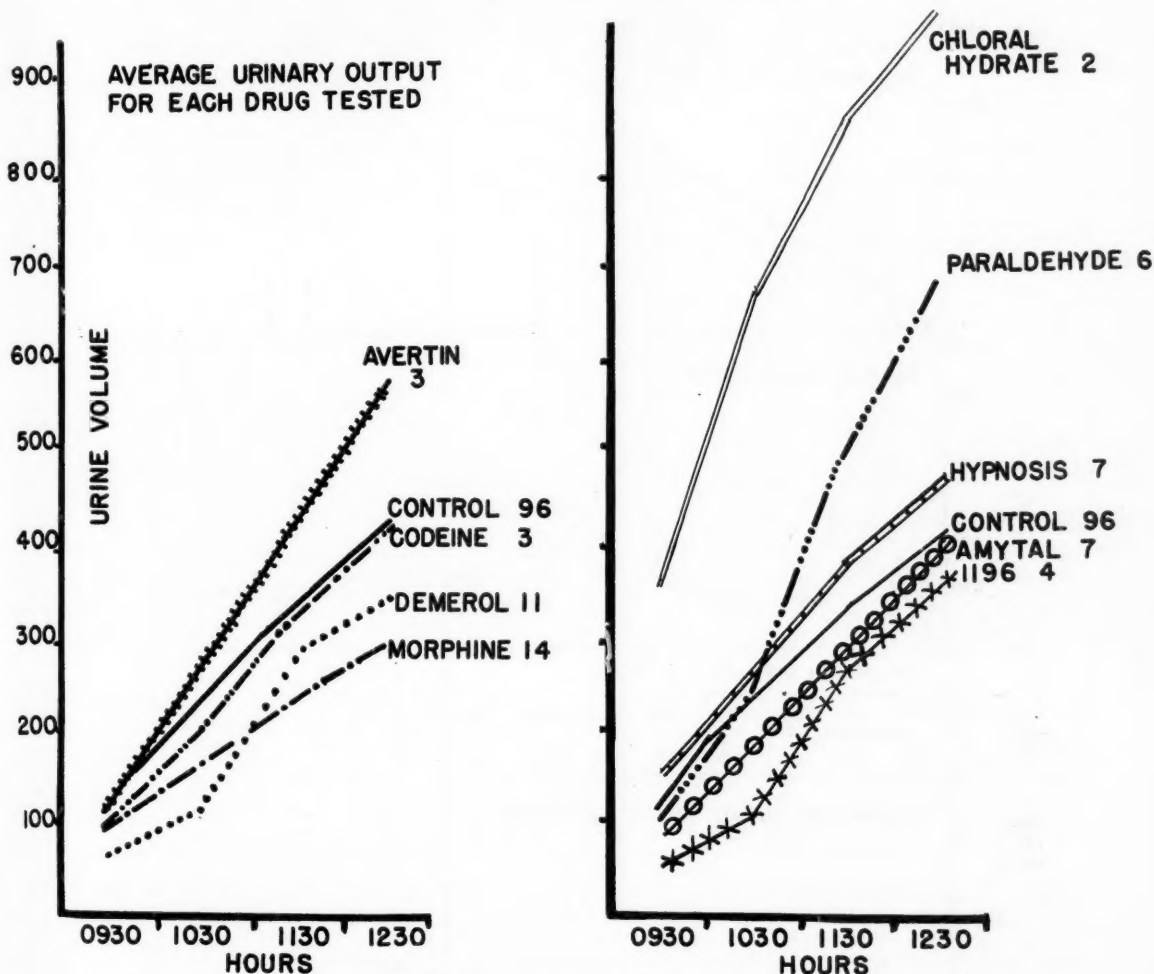


Fig. 6.—Oral fluids. An average of 96 control and 57 experimental observations on 17 subjects. The average response of the several subjects to each drug is plotted against the average of the control observations for the entire group.

Adrenalin antidiuresis, although less marked, is effected primarily by a decrease in renal plasma flow and filtration rate; there is a slight and statistically insignificant increase in tubular reabsorption (Figs. 9 and 10). Thus it appeared that there were two physiological methods for the control of urine volume.

The data obtained in the morphine studies indicated that the decrease in urine volume was obtained both by a decrease in renal plasma flow and an increase in tubular reabsorption. Thus, the antidiuretic effect of morphine is similar to both physiologic agents, but more nearly resembles the action of Adrenalin.

*Other Sedatives.—*

The earlier studies by the oral fluid technique suggested that some depressant drugs were not antidiuretic.<sup>5</sup> This was particularly true of Avertin and paraldehyde (Figs. 4, 5 and 6). It seemed feasible to study these agents by the renal clearance method. Amytal (250 mg.) had no significant effect on any of the clearance features studied, and demonstrated no measurable antidiuretic

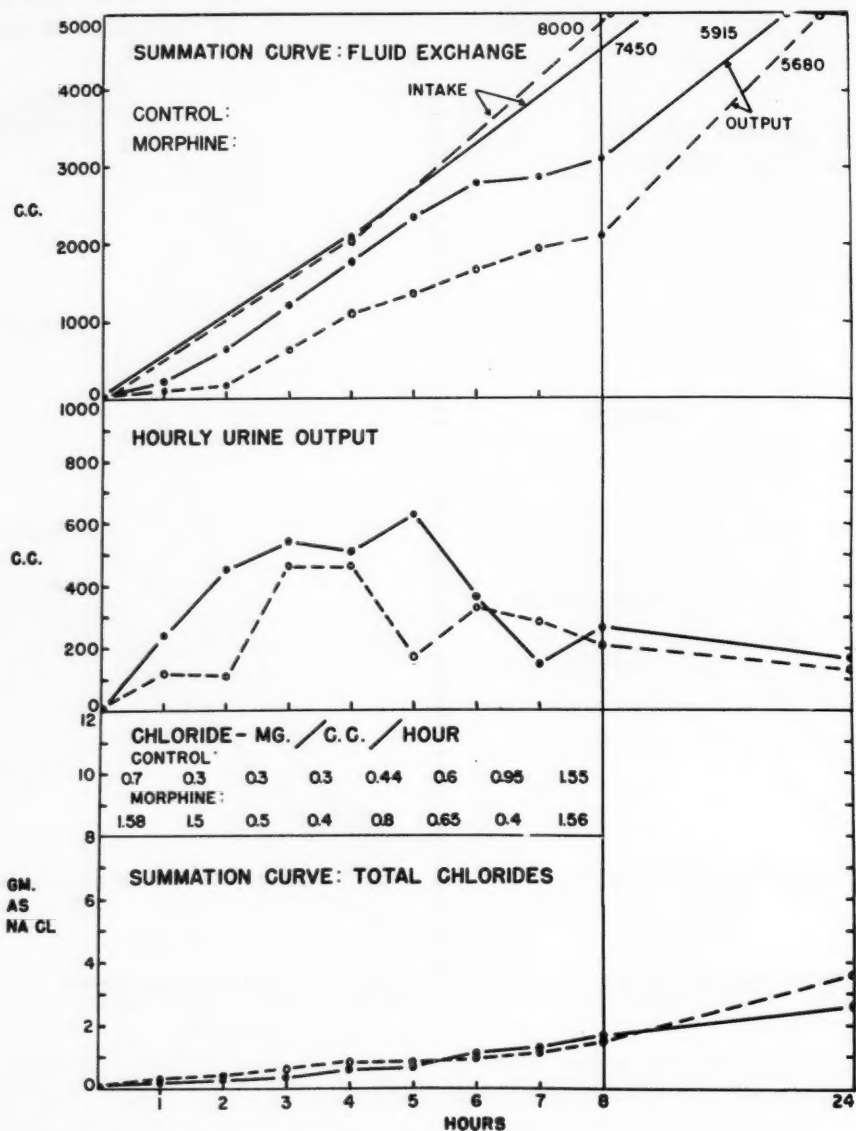


Fig. 7.—See Fig. 2 for description of chart. This patient was 26 years of age and had established diabetes insipidus. She was hospitalized and Pitressin was discontinued until polyuria was re-established. Experiment procedure as described in text. Morphine caused a reduction in urine volume in two such patients studied.

effect (Figs. 11 and 13). Avertin (100 mg. per kilogram) on the other hand, seemed to increase urine volume by means of increased renal plasma flow, and a slight decrease in the reabsorption fraction. These two features tended to produce a slight diuretic response<sup>3</sup> (Figs. 5, 12, and 13).



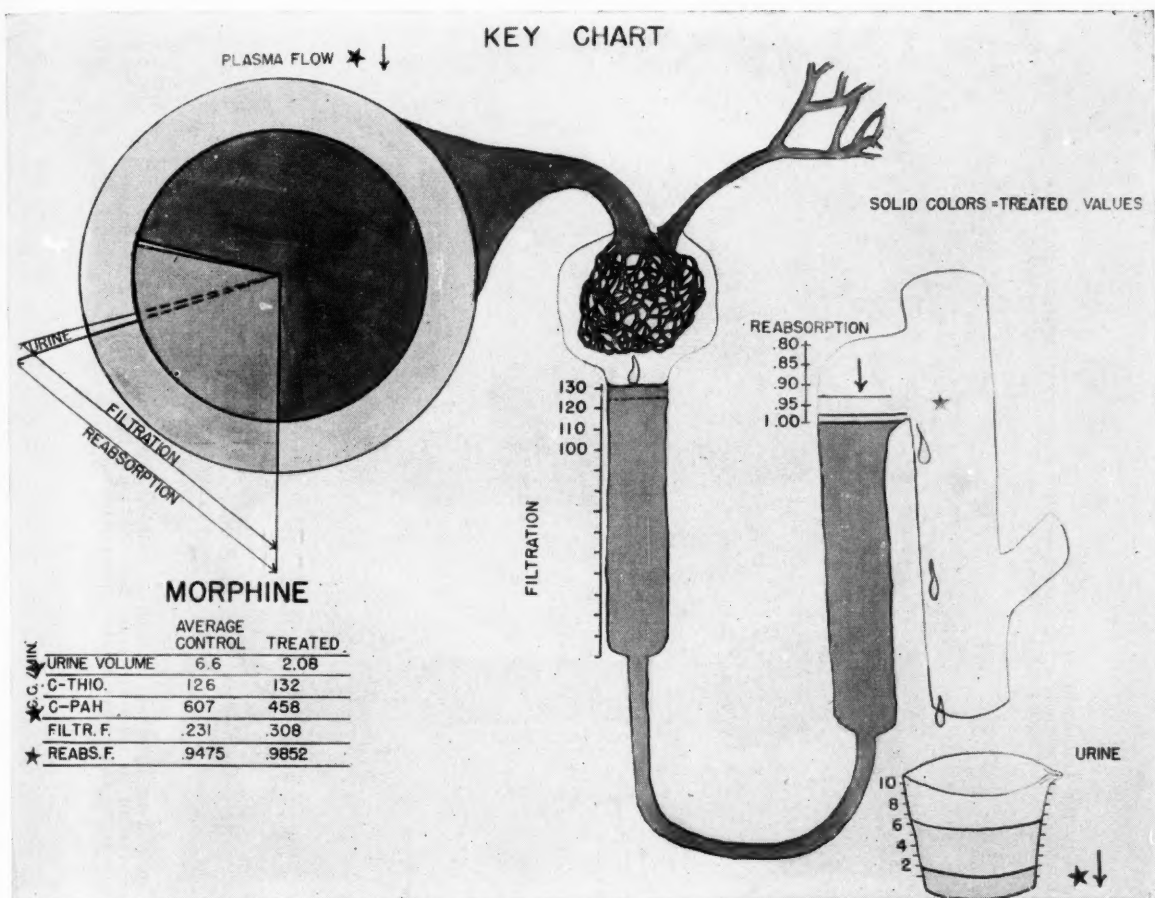


Fig. 8.—A diagram to show the effect of morphine on the intrarenal physiology as determined by the clearance of para-amino-hippurate and thiosulfate. The size of the circle at the left depicting afferent vessel indicates the effective renal plasma flow. The height of column of fluids in tubule indicates filtration fraction. The level of the fluids in collecting tubule indicates the amount reabsorbed and the residual left as urine. The level of fluid in the beaker indicates urine volume. The light shading indicates control data and the dark indicates the changes induced by the experimental agent. The star indicates areas of statistically significant changes. For details of experiment, see text.

Morphine caused a reduction in urine volume by a reduction in renal plasma flow and an increase in tubular reabsorption. This is an average of fourteen patients.

### Comment

These experiments seem to indicate that morphine and some depressant drugs produce an antidiuretic response. This antidiuresis seems to be independent of gastrointestinal absorption, the central depression associated with sleep, and the pituitary hormone, and appears to be an intrarenal change primarily in the vascular bed of the kidney. The similarity of mechanism of morphine and Adrenalin antidiuresis suggests that the morphine effect may be mediated through the adrenal gland.

The significance of these observations in the clinical management of toxemia is yet to be determined. Since the subjects used in these investigations were normal pregnant women, further clinical studies are under way to learn the application of these observations to the management of toxemia and eclampsia.

These studies have demonstrated that the sedatives commonly employed in the management of toxemia and eclampsia vary in their effect on urine volume.

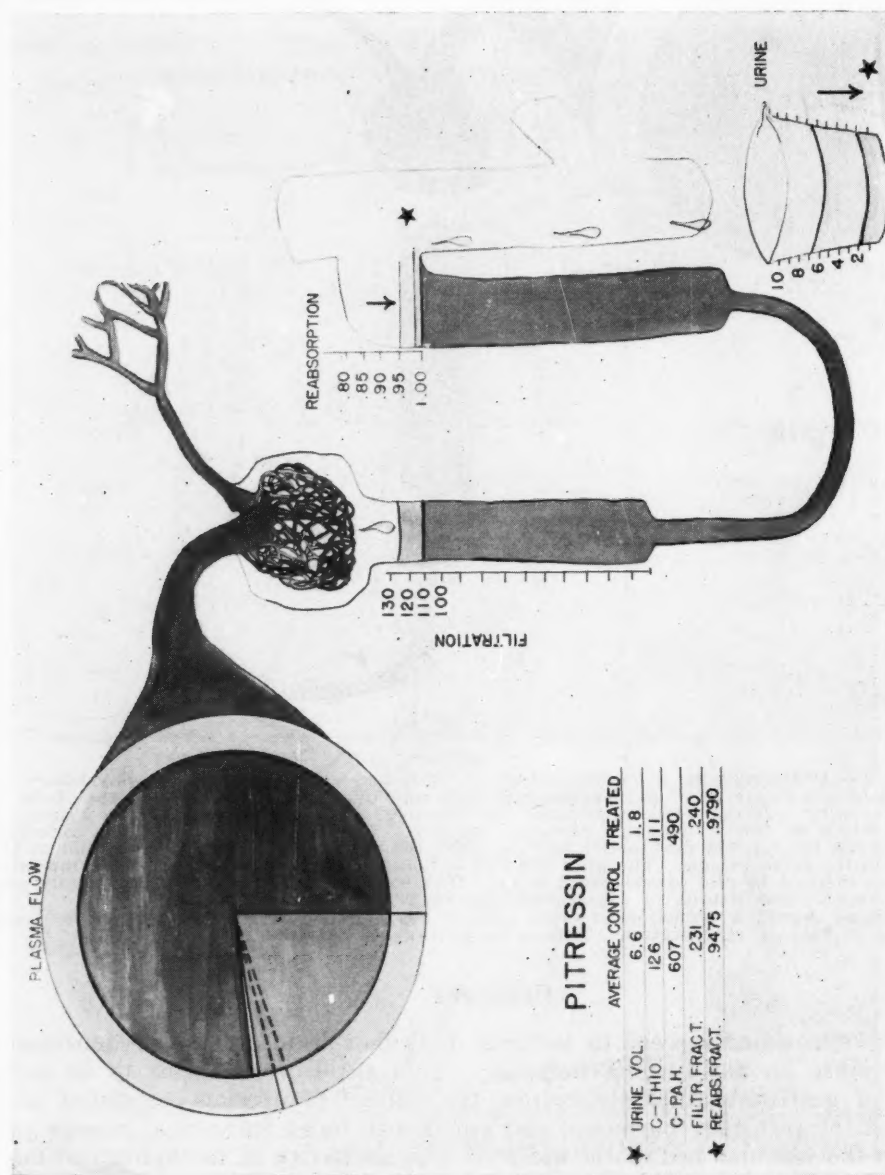


Fig. 9.—See Fig. 8 for description of chart. Pitressin caused a reduction in urine volume primarily by change in reabsorption fraction. The change in renal plasma flow did not prove to be statistically significant by virtue of the variation in control and experimental observations.

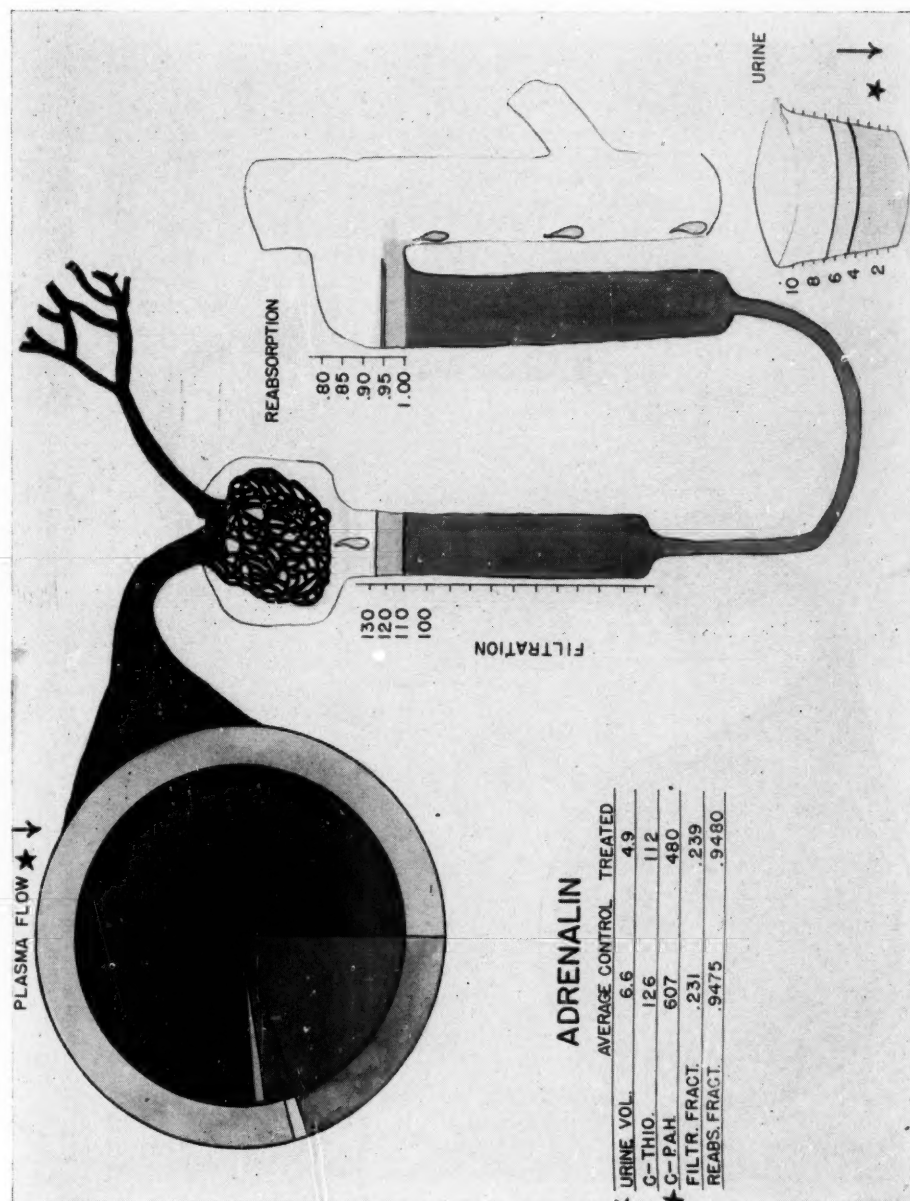


Fig. 10.—See Fig. 8 for description of chart. The antidiuretic effect of Adrenalin is less marked than that of Pitressin. In this average of ten patients the reduction of urine volume and renal plasma flow was statistically significant. There was no change in the reabsorption fraction.

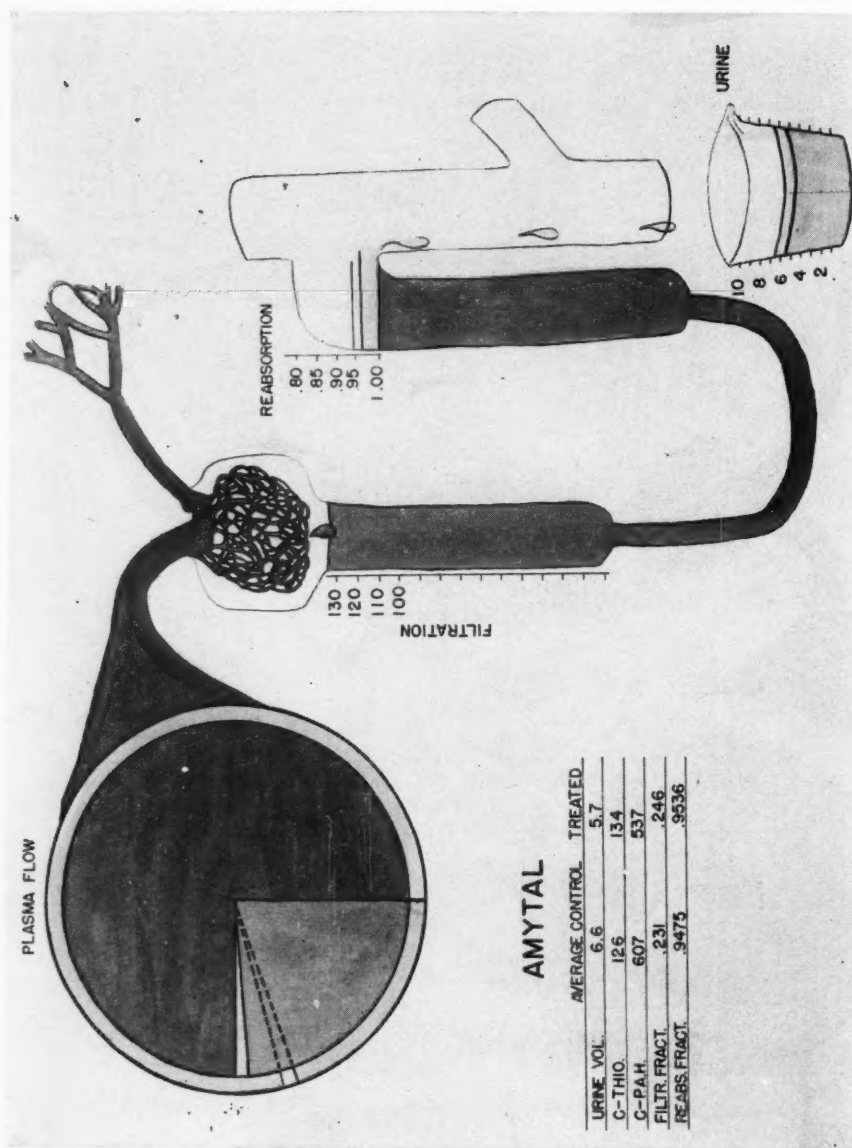


Fig. 11.—See Fig. 8 for description of chart. There is no statistically significant change in these values. Apparently Amytal has little effect on intrarenal physiology. See also Fig. 13.



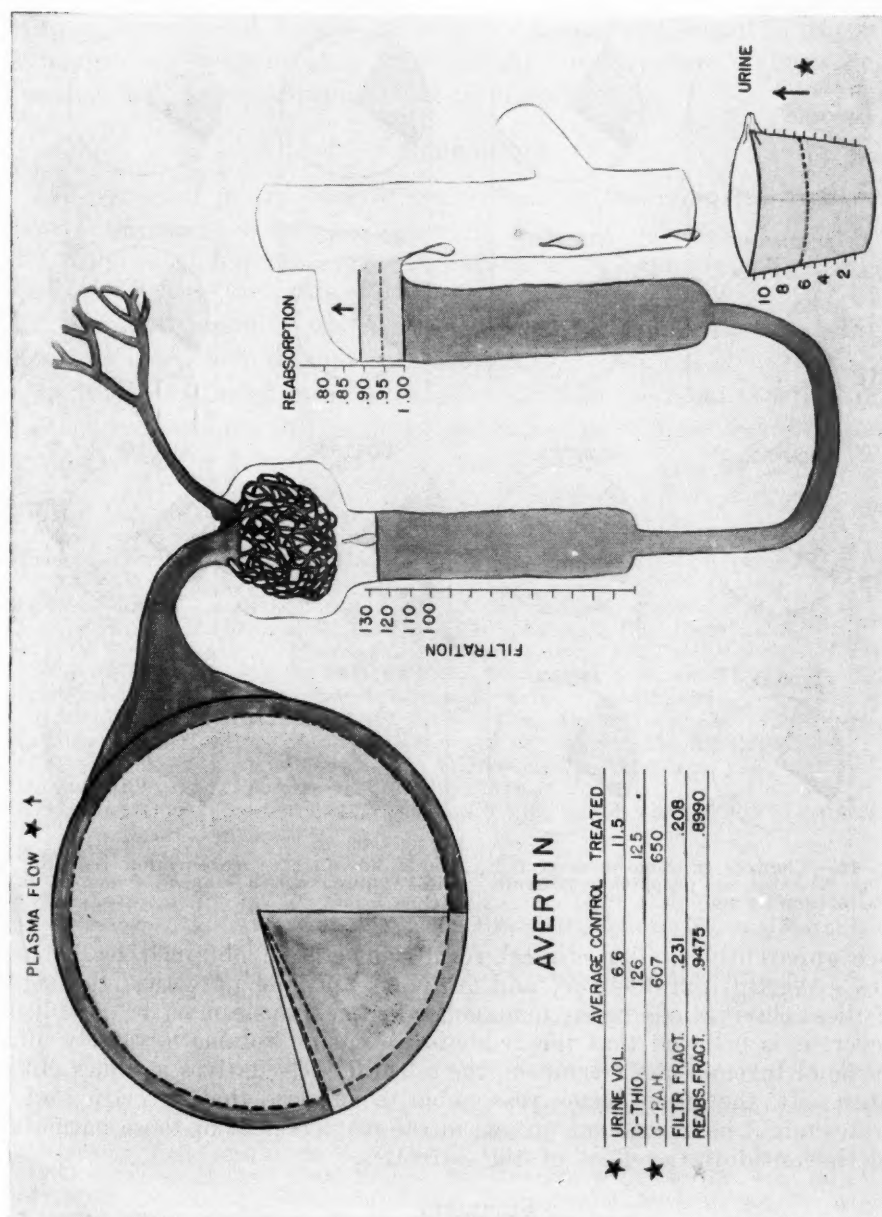


Fig. 12.—See Fig. 8 for description of chart. Note that the increase in urine volume was accomplished by an increase in renal plasma flow (dark circle on outside, see also Avertin on Fig. 13) and a reduction in tubular reabsorption. These figures are statistically significant.

It is of interest that under the same experimental conditions morphine and the other narcotic drugs produce a considerable depression of urine volume, while Avertin in comparable doses causes an increase in urine volume.

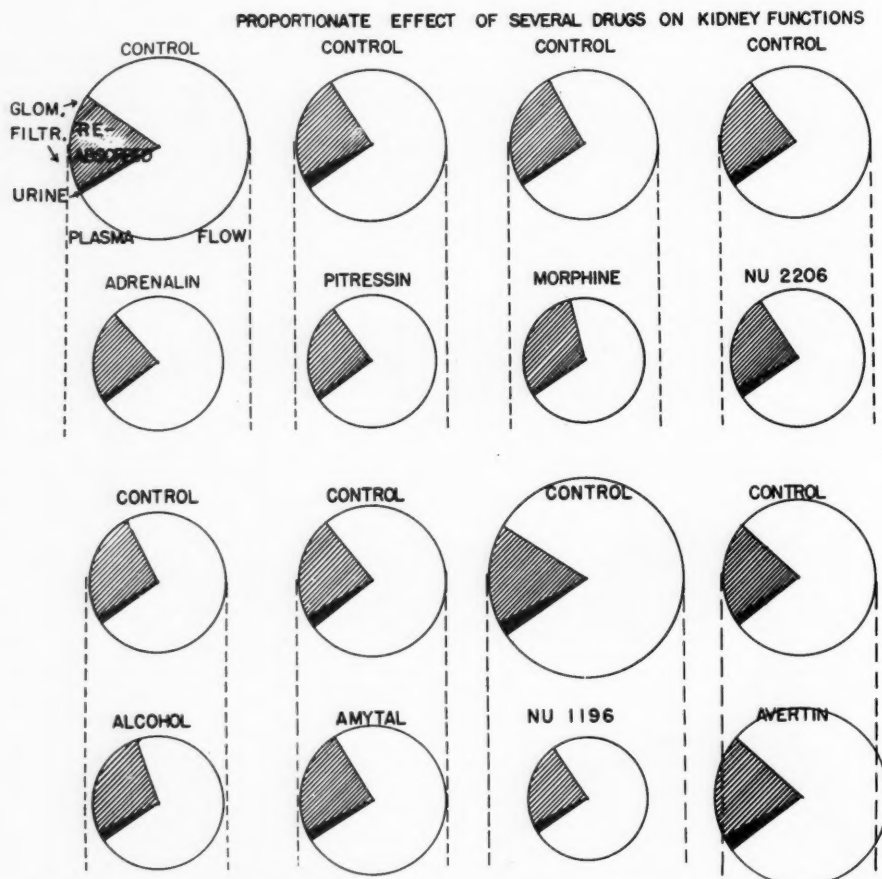


Fig. 13.—Changes in renal plasma flow, glomerular filtrate, reabsorption fraction, and urine value recorded on proportionate scale. These figures are averages of ten to fifteen patients with each agent.

Since apparently similar clinical results have been obtained by both the hypnotics (Avertin, paraldehyde, and Amytal) and the narcotics, the significance of these observations in the management of eclampsia must be established. If, however, it is believed that the reduction of urine volume adversely affects the outcome of toxemia and eclampsia, the selection of sedatives assumes clinical importance. It, therefore, seems reasonable to suppose that Avertin and the barbiturates might have some advantage in the management of these patients by avoiding the antidiuretic effect of the narcotics.

### Summary

These experiments have been designed to throw some light on the mechanism of the effects of morphine and other depressant drugs on renal physiology.

Adrenalin and Pitressin are both antidiuretic and exert a hormonal reduction of urine volume; Pitressin by increasing the reabsorption fraction, and Adrenalin primarily by decreasing the renal plasma flow.

Morphine produces an antidiuretic response by a mechanism similar to that of Adrenalin, namely, a reduction in plasma flow and an increase in reabsorption fraction. These observations suggest that the effect of morphine is probably on the vascular bed of the kidney rather than through the pituitary or by the central depression of sleep.

Since Avertin and Amytal are effective drugs for the control of convulsions in eclampsia, it seems wise to give further consideration to these depressant drugs that *lack* the antidiuretic effect of morphine.

### Conclusions

1. Depressant drugs vary in their effect on the renal function and urine volume of pregnant women.
2. In general, narcotics are antidiuretic while hypnotics (Avertin, paraldehyde, and Amytal) lack this effect.
3. Morphine antidiuresis is accomplished by a decrease in renal plasma flow and an increase in tubular reabsorption.
4. Studies of the effect of these depressants on the renal function of toxemic and eclamptic patients will be necessary before the clinical significance of these observations can be determined.

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### Discussion

DR. FRANK R. LOCK, Winston-Salem, N. C.—Dr. Brown reports the results of a controlled experimental study of the antidiuretic effects of the depressant drugs in the human subject. He has also explored the mechanism of this antidiuresis by application of

standard methods for the direct effect of the drugs upon the renal physiology. The renal clearances of sodium thiosulphate and para-amino-hippurate were used to determine the effect of the depressant drugs upon the tubular and glomerular components and to obtain an estimate of the renal plasma flow in the total kidney function.

The experiments have shown an appreciable suppression of the urinary output following a single injection of morphine in pregnant and nonpregnant women, confirming Dr. Brown's previous studies. He has further made observations on the effects of paraldehyde, Avertin and Amytal and shown that these drugs apparently lack the antidiuretic effect of the narcotics. Avertin may have a slight diuretic response.

The renal clearance studies which are included in this report indicate that the anti-diuretic effect of morphine is the result of a reduced renal plasma flow, a decreased filtration fraction, and an increase in the reabsorption fraction. This observation implies that the effect of morphine is on the vascular bed of the kidney.

Dr. Brown suggests that the selection of the sedative to be used in treatment of toxemia of pregnancy assumes clinical importance, if we may agree that the reduction of urine volume adversely affects the outcome of toxemia and eclampsia. It is generally believed that the renal pathologic change which develops in lower nephron nephrosis is the result of renal circulatory impairment although there is no accord on the mechanism for the renal ischemia. Our observations of patients with oliguria and anuria in toxemia of pregnancy have consistently shown identical clinical and laboratory findings to those observed in other cases of lower nephron nephrosis.

A review of 200 consecutive maternal deaths from toxemia of pregnancy which occurred in North Carolina between August, 1946, and December, 1948, showed that in twenty cases the patient's death was the direct result of oliguria and anuria developing during the course of the disease. In seven additional cases a suppression of the urinary output seriously contributed to the patient's death from another direct cause.

#### IMMEDIATE CAUSE OF DEATH

200 CONSECUTIVE MATERNAL DEATHS FROM TOXEMIA OF PREGNANCY NORTH CAROLINA, AUGUST, 1946, TO DECEMBER, 1948		
<i>Convulsions.</i> —		
Antepartum 27, postpartum 21, combined 22	70	35%
<i>Pulmonary Edema.</i> —		
Antepartum 8, postpartum 19	27	13.5%
<i>Oliguria and Anuria.</i> —		
Contributing to other direct causes 7	20	10%
<i>Hemorrhage.</i> —		
Abruptio placentae 11, postpartum 7	18	9%
Cerebral	16	8%
<i>Coma</i>	12	6%
<i>Other Causes.</i> —		
Hepatic 4, anesthesia 4, embolism 9, etc.	37	18.5%
Total	200	

It is difficult to ascertain from the literature the exact incidence of renal suppression associated with toxemia of pregnancy; it is a grave and significant problem since it was the direct cause of 10 per cent of the maternal deaths from toxemia of pregnancy in North Carolina in 200 consecutive cases.

Morphine is rarely used in the management of severe toxemia of pregnancy in the North Carolina Baptist Hospital. We have been unable to correlate the administration of morphine with the onset of oliguria or anuria in the cases we have observed. However, Dr. Brown has shown that the administration of morphine to a normal patient produces to a small degree the alterations in renal physiology which are identical to those which occur in lower nephron nephrosis and probably in the suppression of urine in toxemia of pregnancy. Therefore, the administration of morphine may further a change in renal physiology which leads to a grave complication in the management of this disease.



The use of inulin for further clearance studies should be considered. The inulin molecule is larger than that of sodium thiosulphate and may be more accurate in the study of disease processes.

Dr. Brown's observations add some evidence in support of our impression that hypnotic drugs are preferable to morphine for the management of severe toxemia of pregnancy.

I hope Dr. Brown will continue his studies of the kidney in pregnancy by these fundamental methods. An accurate evaluation of the effect upon kidney function of the drugs used in the treatment of toxemia of pregnancy and eclampsia will be a valuable contribution to our literature.

DR. CONRAD G. COLLINS, New Orleans, La.—Dr. Brown and his associates have shown that morphine administered to the normal pregnant woman has a definite antidiuretic effect as a result of decreased plasma flow, decreased filtration rate, and increased tubular reabsorption. They have also demonstrated that other sedatives were not antidiuretic, or as antidiuretic as the narcotics. Whether the same results will be obtained in their projected experiments on toxemic and eclamptic patients is a matter of conjecture as other variables, namely, vasospasm, altered electrolytic and metabolic factors, will enter into the picture. We eagerly await the publication of the results of these experiments. At present it is quite difficult to evaluate the clinical significance of the information presented today, and the author has been careful in his conclusions regarding the advisability of the continued use of morphine in the treatment of eclampsia. Morphine is the sheet anchor of the therapeutic regimen advocated by Mengert. Since Jan. 1, 1946, through July 1, 1949, twenty-four cases of eclampsia have been observed on the Obstetrical Division of the Tulane Unit at Charity Hospital in New Orleans. In all except one case, morphine was administered, the dosage being from  $\frac{1}{6}$  to  $\frac{3}{4}$  grain. As most of the cases of eclampsia we see are sent to us from the outside, it is very difficult to ascertain whether or not these patients have had morphine prior to their admission to the hospital. Some have and some have not.

In eight of this series, it was found necessary to continue the administration of morphine in the second and third twenty-four hour periods. Three women, one with postpartal eclampsia, died while in the hospital and another died three months later from cerebral degeneration. Whether morphine contributed in any way to these unfavorable results could not be determined from the patients' charts; However, none died in anuria, although circulatory collapse, pulmonary edema, and oliguria were manifest.

For years the mortality rate of eclampsia at Charity Hospital in New Orleans has hovered around 10 per cent. Certainly, in the future, should the findings described today hold true in the toxemic and eclamptic patient, we will drop morphine from our therapeutic armamentarium. However, should it be shown, in toxemia and eclampsia, that, though the barbiturates produce no antidiuretic effects in the normal pregnant woman, and do so in the toxic, then, in addition to barbiturates, morphine will continue to be used on our service.

DR. WILLIAM F. MENGERT, Dallas, Tex.—We have used morphine in the treatment of eclampsia for a long time. Some three or four years ago we started our present regimen in the treatment of eclampsia and since that time have treated over thirty convulsive women, of whom twenty-nine have walked home. One died shortly after admission to the hospital. These women received amounts of morphine seldom less than  $\frac{3}{4}$  of a grain, and frequently as high as 3 or 4 grains of morphine. The eclamptic phase, the convulsive phase of eclampsia, is an extremely short period, since the woman either recovers or dies in a matter of hours. Since morphine has proved to be, over the years, such a satisfactory drug clinically, I am wondering if the decrease in urinary filtration for a matter of a few hours is a feature sufficiently important to impel us to discard a drug which otherwise has given such excellent results.

DR. LESTER A. WILSON, Charleston, S. C.—I have used morphine for many years. As the years have gone by, I have increased the amount of morphine used in these patients. With larger doses, I have noted a higher incidence of anuria: Clinically this confirms Dr. Brown's findings. However, I should not like to let this paper go by without the comment

that anuria is a relatively infrequent complication compared to the numerous other complications and sequelae of eclampsia, many of which lead to death; and that morphine provides so much better management of the patient in convulsions that it is questionable whether we should ban this drug because of one slight defect.

DR. L. A. CALKINS, Kansas City, Kan.—Since this is a study of physiology rather than of pathology, I would like to ask Dr. Brown one question. His studies, as I interpreted them, were carried on through approximately twenty-four hours, at the end of which time the total urinary output was still depressed. Can he give us any figures as to when, if ever, following a single dose of morphine, the urinary output did catch up to normal?

DR. EDWARD L. KING, New Orleans, La.—This paper is interesting from a historical point of view. When I started my internship forty years ago, the surgeons in the Charity Hospital were very much opposed to giving preanesthetic morphine because the contention was that postoperatively it reduced the urinary output. However, in those days the anesthetic was always ether, blood transfusion was practically unknown, surgery was more traumatic than at present, and biochemistry was a closed book. Clinical observation had to suffice.

We have, as Dr. Collins brought out, a fair number of eclamptic patients brought in from a radius of 100 miles, and most of them have had morphine before they reach us. We have used Sodium Amytal alone. It worked well except for a precipitous drop in blood pressure which apparently led to an increase in pulmonary edema that may have possibly contributed to death in a few cases. We still employ morphine. However, I think it would be wise to reduce or eliminate morphine in those cases which present oliguria while we may still use it in those patients who are putting out an ample supply of urine.

DR. BROWN (Closing).—I am very pleased with such generous discussion of this physiologic report. We are well aware that morphine has become, and perhaps should remain, the therapy of choice in patients with convulsions. It is readily available, is easily administered, and is effective. I have moved to the "eclamptic belt" (Arkansas) where I can pursue these studies, and as Dr. Collins has said, find out if they are applicable to the clinical management of these patients.

In answer to Dr. Calkins' question, the majority of these patients were not followed for twenty-four hours. In general, the urine volume began to catch up at the end of eight hours. The duration of depression of a single injection of morphine is probably much less than six or eight hours in the average patient.

## A STUDY OF THE EMOTIONAL REACTIONS DURING LABOR\*

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EVERY human experience contains elements of emotional, mental, physiological, and physical nature. That the emotional element is a major factor in pregnancy and labor cannot be denied. In 1888, S. C. Busey<sup>1</sup> stated, "The manifestations of suffering are more influenced by mental and emotional than the physical conditions. Delicate and feeble women often pass through the travail of labor with composure and heroism, whilst the robust and healthy often exhibit their suffering in the most exaggerated manner." Forty-four years later, Fairbairn<sup>2</sup> wrote, "Many women approach pregnancy and labour with a view distorted by what they have heard or seen of the terrors of labour. These difficult cases require careful consideration from the psychological side and will benefit by confidential talks in which may be revealed hidden dreads that might interfere with normal function."

More recently, Grantly Dick Read<sup>3</sup> has stimulated interest in the emotional aspects of childbirth. In 1944 he wrote in his book, "Childbirth Without Fear,"<sup>4</sup> that normal, physiological labour should be virtually painless. His contention is that the fear of delivery produces tension which in turn produces pain, and that this fear-tension-pain sequence can be prevented by education and training during pregnancy for active participation in labor. The terms "physiological" and "natural" childbirth have been applied to pregnancies and labors conducted in this manner.

There are enthusiastic proponents of the principle that fear produces tension and tension produces pain. This is true, but at the same time there is an appreciable number of women who are unable to dispel their fear and develop the controlled relaxation that is necessary for the success of this method; for childbirth, even today, is swathed in superstition, folklore, misinformation, and horror tales—fused together to influence the woman in labor. Helene Deutsch<sup>5</sup> points out, "like the *vehini-hai* of the Marquesans, the voice of fear . . . speaks in the soul of modern woman too: 'You will die in childbirth, little mother.'"

Because of the renewed interest in the emotional aspects of labor, because many women fail to experience natural childbirth successfully, because of the complexity of the unconscious factors in behavior motivation, and because of the confusion arising from folklore and superstition, it was decided to study a group of apparently normal women who had had no formal emotional or educational preparation for labor.

\*Presented at a meeting of the Utah Obstetrical and Gynecological Society, Salt Lake City, Oct. 13, 1949.

Such a study is made difficult by the varying approaches to the problem. Emotional reactions during labor are considered unimportant or are completely ignored by many physicians. Enthusiasts of natural childbirth give the impression that those women who fail in, or indicate disapproval of, this method are of low intelligence, have intrinsic psychiatric problems, or are otherwise abnormal. This is not necessarily true. Such an attitude does not take into consideration the normal variation within the personality. Some obstetricians focus their attention upon the mechanics of labor and ignore the patient's personality. Others, disturbed by expressions of unpleasant emotions and sensations during labor, attempt to eliminate them by complete anesthesia and amnesia. That this does not solve the problem is evidenced by the patient who, from the birth of her first to the birth of her second child, was frequently awakened by nightmares filled with unremembered, terror-ridden content. At the birth of the second child, and while partially anesthetized, she screamed, "There they are! The lights! The people! They said they didn't hurt me but they did! They did! I just didn't remember!" Subsequently it was learned that as a primipara under the influence of scopolamine, she had been subjected to pain, manipulation, and forceps delivery. The experience, buried deep in the subconscious, had been producing frequent nightmares and definitely contributed to unpleasant emotional reactions during the second labor. This indicates that an evaluation of labor must consider the unconscious as well as the conscious motivating factors. Medication may release unconscious conflicts and fears and allow expression of the basic personality. Behavior and emotions with or without medication should be evaluated as they occur.

It is the purpose of this paper to present the results of a study which was designed to assess more adequately the factors which influence the emotional reactions during labor. Suggested criteria for evaluating an individual case will also be presented.

### Material and Procedure

Five hundred patients were studied. Of these, 32 per cent were primiparas and 68 per cent were multiparas. They were private patients receiving prenatal and obstetrical care from physicians practicing in a community of approximately 50,000 population. Some had received instruction from their doctors, mothers or friends; but there was no organized indoctrination or preparation for labor. As each patient entered the hospital, and before medication was given, she filled in a questionnaire designed to determine her attitude toward the experience. She was asked if she had any anxiety or fear, and if so, exactly what. Her knowledge of what to expect was ascertained. If she had had previous labors, she was asked how she felt about the experience. She was also asked if she desired to participate in the present labor and to be aware of contractions, or if she preferred to be "clear out" with medication. Her conduct throughout the labor, the length of labor, medication used, complications and unusual events encountered were observed, recorded, and an evaluation made.

Following labor, after the effects of medication had worn off, the patient's own evaluation of her labor was obtained. She was asked how she felt about the recent experience. Was she satisfied, happy, and contented; or did she have some vague, unpleasant feelings of unrest or discomfort. Specific statements



were obtained as to what she thought contributed most toward the pleasantness or unpleasantness of the labor. To evaluate better the emotional factors involved, detailed psychiatric examination was made when indicated.

The following criteria for the evaluation of the labors were used:

*Class I. Excellent.—*

1. The patient's conduct during labor, with or without medication, is always under her control although she may demonstrate normal, controlled apprehension and curiosity.
2. The patient is able to rest quietly between contractions. During the first stage, she may demonstrate some increase in mental and physical activity; but this is always within control, is purposeful, and does not give the feeling or impression that it is overwhelming, or that the anxiety and fear it covers are all engrossing.
3. Throughout labor, she is free from any but the normal sounds of exertion, comments, and expletives which often accompany active participation.
4. She is free from cries of terror, excessive bed-gripping, wringing of hands, writhing about, etc. Dreams and hypnagogic hallucinatory experiences may occur at any time and especially with the administration of anesthesia, but they are not disturbing to the patient and may even be of a pleasant nature.
5. There are no unpleasant emotional reactions post partum, such as the feeling that she has missed something, infant rejection, depression, anxiety, etc. The patient is cheerful, contented, pleased, and is satisfied with herself and the labor experience.

*Class II. Good.—*

1. The patient's behavior during labor, with or without medication, is out of her control only occasionally and to a minimal degree. Control is easily regained with support from her attendants and/or medication.
2. The patient rests most of the time between contractions and behavior is appropriate. She may fuss and complain of discomfort during the second stage, but to a minimal degree.
3. Apprehension is more severe than in Class I, but still controlled.
4. The patient experiences a minimal degree of unpleasant emotions and sensations. There may be sounds of exertion, comments, and expletives indicating this.
5. The patient cries out from time to time with contractions and demonstrates a minimal amount of fussing and tension. She is still free of bed-gripping, writhing, wringing of hands, etc. Dreams and hypnagogic hallucinatory experiences which may occur are not disturbing.
6. There are no unpleasant emotional reactions post partum. Though the patient may have some unpleasant memories of discomfort, she is cheerful, contented, pleased, satisfied with herself, and does not think of the labor as an unpleasant, fearful experience.

*Class III. Fair.—*

1. The patient, with or without medication, loses control of her conduct and behavior during 50 per cent of the labor time.
2. The patient rests between contractions during the first stage of labor but demonstrates muscle rigidity, tension, fear, and moans with contractions.
3. The patient shows moderate to marked apprehension and fear, doubt, and ignorance of the labor process. Behavior and demeanor indicate definite unpleasant emotional and physical sensations.
4. She is unable to control outcries, moaning, muscle rigidity, wringing of hands, etc., 50 per cent of the time. During the second stage and toward the end of labor, she is completely out of control. A patient who has conscious control of her behavior and reactions and appears to belong to Class I or Class II may fall into this Class after medication is given and deeper unconscious motivating forces are allowed expression.
5. Dreams and hypnagogic hallucinatory experiences are frequent and disturbing, and the patient often reacts more to these than to the reality of the labor experience.
6. Post partum, this patient may feel cheerful, contented, pleased, satisfied, etc., but also feels that labor is a very painful and unpleasant experience. Often she is not anxious to repeat it. Unpleasant emotional reactions often persist and develop post partum,

*Class IV. Poor.—*

1. The patient, with or without medication, shows complete lack of control of behavior and emotions from the onset of contractions.
2. She is unable to rest or control her behavior and activity during the entire labor.
3. Apprehension and fear are marked and constant. There is no evidence of compensatory or adjustment mechanisms acting to bring emotions and behavior under control.
4. The patient cries out with contractions from the onset of labor. Muscle rigidity, tension, wringing of hands, writhing about, gripping of objects, etc., occur throughout labor. She screams out for her mother, husband, or other persons, and for help. Dreams and hypnagogic hallucinatory experiences are frequent and disturbing.
5. The patient, with or without medication, is unable voluntarily to participate in the labor experience. Often, she is unable to make use of assistance and support offered by attendants. She may even reject them.
6. Post partum, she remembers the labor experience as something horrible, never to be repeated. Pleasant and satisfying sensations are submerged by the memories of unpleasantness, frustration, and pain. Unpleasant emotional reactions persist and develop post partum. An occasional patient in this group may feel and express satisfaction and contentment post partum, but reactions during labor are obviously of Class IV and she has deep unconscious behavior motivating factors of which she is unaware.

**Results and Comments**

Table I indicates the classification of the labors according to the criteria adopted for the study. Fifty-six per cent of all patients were in Class I. Following delivery these patients were completely contented, happy, and satisfied with the experience and had no unpleasant memories. They felt normal attachment to their babies and thought the labor experience was thrilling and pleasant. Thirty-two per cent were placed in Class II. These patients demonstrated minimal fear, tension, or other emotional difficulty during labor. Combining these two classes indicates that 88 per cent of the labors were satisfactory according to these criteria. Goodrich and Thoms,<sup>6</sup> in a clinical study of natural childbirth, found that 80.7 per cent of 156 patients had satisfactory labors. The two studies are not comparable, however, for in Thoms' study, the patient's need or rejection of medication was used as an important criterion of evaluation. It is interesting to note that approximately the same percentage of patients had a satisfactory labor, and that about 90 per cent of these patients in both studies were completely satisfied with the manner in which the labor was conducted (Table V).

A further study of Table I indicates that 12 per cent of the patients had unsatisfactory labors. Eight per cent were placed in Class III and 4 per cent in Class IV. These figures also approximate the per cent (19.3) of unsatisfactory labors in Thoms' study.

TABLE I. CLASSIFICATION OF EMOTIONAL REACTIONS DURING LABOR

	CLASS I 282 PATIENTS (PER CENT)	CLASS II 158 PATIENTS (PER CENT)	CLASS III 41 PATIENTS (PER CENT)	CLASS IV 19 PATIENTS (PER CENT)	TOTAL 500 PATIENTS (PER CENT)
Primiparas 160 Patients	51	32	12	5	32
Multiparas 340 Patients	59	32	6	3	68
Total (500 patients)	56	32	8	4	100
	88% (440 Patients) Satisfactory		12% (60 Patients) Unsatisfactory		

Table II shows the patient's own antepartum evaluation of her emotions. Thirty-two per cent of primiparas who ultimately were evaluated as Class I patients acknowledged the presence of some fear and anxiety, while 68 per cent and 63 per cent of those placed in Classes III and IV were aware of emotional tension. The same trend is noted in the multipara except that it is even more impressive and illustrates well the fact that as anxiety and fear increase, the emotional response during labor becomes increasingly unpleasant and unsatisfactory.

TABLE II. SUBJECTIVE ANTEPARTUM EVALUATION. PRESENCE OF ANXIETY OR FEAR (500 PATIENTS)

	PRIMIPARAS (160 PATIENTS)				MULTIPARAS (340 PATIENTS)				TOTAL
	CLASS I 81 PTS.	CLASS II 52 PTS.	CLASS III 19 PTS.	CLASS IV 8 PTS.	CLASS I 201 PTS.	CLASS II 106 PTS.	CLASS III 22 PTS.	CLASS IV 11 PTS.	500 PATIENTS
No	68%	46%	32%	37%	74%	53%	32%	18%	60%
Yes	32%	54%	68%	63%	26%	47%	68%	82%	40%

Table III indicates what consciously accounts for this fear and tension in these patients. Forty-five per cent were aware of the fear of death, hemorrhage, pain, long labor—indicating fear for self. Fear that the infant would be abnormal or injured during delivery accounted for 43 per cent of the anxiety. A vague, free-floating anxiety, and not knowing what to expect in labor were less frequently listed. Still less frequently mentioned items were fear of how she would behave in childbirth (fear that she would not do “the most important thing in her life” in a creditable manner), and fear of hypodermic injections. This table, also, indicates that, as fear and anxiety increase, so increase unpleasant emotional reactions.

TABLE III. SUBJECTIVE ANTEPARTUM EVALUATION. ANXIETY AND FEAR PRODUCING FACTORS (199 PATIENTS)

	PRIMIPARAS (72 PATIENTS)				MULTIPARAS (127 PATIENTS)				TOTAL
	CLASS I 26 PTS.	CLASS II 28 PTS.	CLASS III 13 PTS.	CLASS IV 5 PTS.	CLASS I 53 PTS.	CLASS II 50 PTS.	CLASS III 15 PTS.	CLASS IV 9 PTS.	199 PATIENTS
Fear for self— hemorrhage, death, pain, long labor	31%	18%	85%	40%	45%	44%	60%	89%	45%
Fear of abnormal or injured baby	35%	50%	31%	40%	51%	34%	53%	56%	43%
Fear—vague, free- floating	12%	14%	23%	20%	11%	6%	0	0	11%
Not knowing what to expect	23%	18%	0	20%	2%	0	0	0	7%

The patient's attitude toward labor, Table IV, also indicates the trend of the emotional reactions. As knowledge of what to expect during labor diminishes, unsatisfactory labors increase. Eight-eight per cent of the primiparas in Class IV admitted complete lack of knowledge of childbirth, while only 35 per cent of those in Class I expressed ignorance. Only a small percentage of the multiparas felt that they did not know what to expect, but their attitude toward previous labors was important. As the number of multiparas remembering previous labors as being unpleasant and undesirable increased, the number falling into Classes III and IV also increased. However, 37 per cent

of the multiparas placed in Class I felt that labor was painful and unpleasant, but still showed no evidence of abnormal emotional response. This indicates that there is something besides knowledge of the process and absence of fear that contributes to satisfactory labor. This point will be discussed later.

The patient's attitude toward active participation in labor is also revealing. Thirty-seven per cent of Class I multiparas desired anesthesia, while 99 per cent of those in Class IV desired it. This indicates that some patients consider anesthesia as a means of escape from the unknown, fear, and pain. However, the Class I multiparas who did not want to participate actively in labor and who desired medication were mature, normal women free from uncontrollable fear and anxiety. The usual comment made by many of these women was, "I have experienced childbirth with and without medicine and I see no reason for unnecessary pain. I want some relief." There is no doubt that fear and tension increase the demand for medication, but all need for it is not on this basis for, as Helene Deutsch points out, "By attributing labor pains to fear alone . . . underestimates their organic causes."

Table IV also indicates that there is a considerable number of patients (24 per cent) who, without indoctrination, are aware of the emotional advantages of active participation in labor. An additional 15 per cent desiring to be awake but with reservations can be added to this group. It is interesting to note that a larger proportion of primiparas than multiparas were undecided with regard to active participation in labor. This correlates with the greater proportion of primiparas who had no knowledge of what to expect and who had not been influenced by previous labor experiences.

TABLE IV. SUBJECTIVE ANTEPARTUM EVALUATION. KNOWLEDGE OF AND ATTITUDE TOWARD LABOR (500 PATIENTS)

	PRIMIPARAS (160 PATIENTS)				MULTIPARAS (340 PATIENTS)				TOTAL 500 PTS.
	CLASS I 81 PTS.	CLASS II 52 PTS.	CLASS III 19 PTS.	CLASS IV 8 PTS.	CLASS I 201 PTS.	CLASS II 106 PTS.	CLASS III 22 PTS.	CLASS IV 11 PTS.	
No knowledge of labor	35%	33%	63%	88%	1%	3%	9%	—	14%
Previous labor unpleasant					37%	63%	66%	67%	49%
Previous labor pleasant					63%	37%	34%	33%	51%
<i>Desire to Participate in Labor.—</i>									
No	32%	43%	21%	29%	37%	49%	68%	99%	41%
Yes	32%	20%	21%	29%	31%	13%	14%	—	24%
Undecided	24%	27%	37%	42%	15%	19%	9%	1%	19%
Partial	12%	10%	21%	—	17%	19%	9%	—	15%

The patient's own postpartum evaluation of her labor experience is of interest (Table V). One hundred per cent of the patients in Class I were completely contented, pleased, and happy, and thought of labor as a desirable experience. Ninety-four per cent of the patients in Class II also felt this way. Those who did not had definite and justifiable reasons for not doing so. Six of these patients had stillborn infants; four objected to anesthesia given—two low saddle block, two ether; two had abnormal presentations and prolonged labor; one was left in the labor room for seven hours and felt much neglected; one precipitated on the way to the hospital; and one was unwed. Post partum, only three patients in this group complained of painful contractions during labor and two of depression without apparent reason.



Twenty-one per cent of all the patients were completely satisfied after delivery but had no specific factors to list as contributing to or detracting from the satisfaction they felt. Women in this group were probably motivated to have babies and to accept labor without demonstrating abnormal emotional reaction regardless of the manner in which it was conducted. The remainder of the patients having satisfactory labor repeatedly listed two or three definite reasons for absence of unpleasant emotional upheaval. Sympathetic, constant care with repeated explanations was most frequently mentioned. The patient who was met at the door of the labor unit; asked pertinent questions concerning her labor—the estimated date of confinement, onset, frequency, and duration of contractions; whether or not membranes were ruptured, etc.; and who was personally escorted to the preparation and labor rooms, observed and checked frequently, given adequate explanation as to her progress in labor; and who was made to feel that the attendants had personal interest in her was most profuse in her praise of the manner in which the labor was conducted. She did not hesitate to list this as the most pleasant memory of her labor experience. Twenty-two per cent of all patients felt that this contributed most toward the reduction of anxiety and fear. There is nothing new in this approach, but all too frequently labors lack this personal attention.

TABLE V. SUBJECTIVE POSTPARTUM EVALUATION. EMOTIONAL REACTION TO LABOR  
(500 PATIENTS)

	PRIMIPARAS (160 PATIENTS)				MULTIPARAS (340 PATIENTS)			
	CLASS I 81 PTS.	CLASS II 52 PTS.	CLASS III 19 PTS.	CLASS IV 8 PTS.	CLASS I 201 PTS.	CLASS II 106 PTS.	CLASS III 22 PTS.	CLASS IV 11 PTS.
Patients happy, pleased, con- tent, satisfied	100%	94%	79%	50%	100%	93%	68%	56%
Total	149 or 93%				321 or 94%			

FACTORS CONTRIBUTING TO SATISFACTORY LABORS

	PRIMIPARAS (160 PTS.)		MULTIPARAS (340 PTS.)		TOTAL (500 PTS.)	
	NO.	%	NO.	%	NO.	%
No specific reason	28	18	78	23	106	21
Sympathetic care with ex- planation and personal interest in patient	22	14	76	22	108	22
Relief from pain	34	21	51	15	85	17
Hearing baby cry, feeling baby born	21	13	44	13	65	13
Just because labor over	11	7	36	11	47	9.4
Feeling of accomplishment	12	8	23	7	35	7
Just because she has baby	11	7	18	5	29	5.8
Presence of husband	8	5	8	2	16	3.2
Being awake during labor	3	2	6	1.5	9	1.8

The next most frequently mentioned factor was the relief from painful contractions obtained through medication. Seventeen per cent of all patients listed this and it will be commented upon later.

As often mentioned as the relief from pain was the thrill of hearing the baby cry and the feeling of his being born. This is obviously an important factor in the thrill of childbirth. To the woman who has been looking forward to this moment for many months and years, the sensation of being the all-important character in the dramatic event and the relief felt when it is sensed that the

baby is normal are overwhelmingly thrilling. Other factors less frequently mentioned as contributing to satisfactory emotional responses during labor were the feeling of having accomplished a great thing, presence of the husband during labor, relief in having the labor over, the possession of an infant, and being awake during labor. Attention paid to these apparently minor items contributes much toward a satisfactory labor.

Table VI presents those factors listed by the patients post partum as contributing most to unpleasantness during labor. Thirty-eight per cent of primiparas in Class I and 75 per cent of those in Class IV listed painful contractions as the most unpleasant part of childbirth. Figures for the multipara group are not as impressive but still indicate the importance of this factor. That there is organic cause for the pain is indicated by the fact that 38 per cent of primiparas in Class I felt pain. At the same time, it is impossible to state that painful contractions were the only factor contributing to the emotional reactions of the primiparas in Class IV. It is a well-recognized psychological truth that emotional conflict will find expression through the body. During labor no better organ for this expression exists than the contracting uterus. Forty-two per cent of all patients stated they felt labor pain. Since only 12 per cent of all patients had unsatisfactory labors, it again indicates that patients having satisfactory labors feel pain on an organic basis. Emotional upheaval, fear, and anxiety can influence this organic pain, but to state that it is entirely on this basis is oversimplifying the problem.

TABLE VI. SUBJECTIVE POSTPARTUM EVALUATION. FACTORS CONTRIBUTING TO UNPLEASANT EMOTIONAL REACTIONS DURING LABOR (500 PATIENTS)

	PRIMIPARAS (160 PATIENTS)				MULTIPARAS (340 PATIENTS)			
	CLASS I 81 PTS.	CLASS II 52 PTS.	CLASS III 19 PTS.	CLASS IV 8 PTS.	CLASS I 201 PTS.	CLASS II 106 PTS.	CLASS III 22 PTS.	CLASS IV 11 PTS.
Pain	38%	68%	68%	75%	19%	42%	59%	54%

	PRIMIPARAS (160 PTS.)		MULTIPARAS (340 PTS.)		TOTAL (500 PTS.)	
	NO.	%	NO.	%	NO.	%
Pain	83	52.0	127	37.0	210	42.0
Manipulation, instrumentation, rectals, suturing	17	11.0	45	13.0	62	12.0
Anesthesia	9	6.0	15	4.0	24	5.0
Labor "hard," dead infant	3	2.0	13	4.0	16	3.0
Previous unpleasant labor						
Comments of attendants	5	3.0	5	1.0	10	2.0
Stirrups, being strapped down	4	2.5	4	1.0	8	1.6
Fear of Rh, cesarean section, other unusual event	4	2.5	4	1.0	8	1.6
Fear of doctor's not being present	2	1.2	6	1.7	8	1.6
Precipitate labor	--	--	7	2.0	7	1.4
On delivery table too long	1	0.6	6	1.7	7	1.4

An appreciable number of patients (12 per cent) felt that manipulation, instrumentation, suturing, and rectal examinations contributed more to unpleasantness than any other factor. Other complaints included undesired anesthesia which was forced upon the patient, unpleasant comments and scolding by attendants, a sensation of helplessness when strapped to the stirrups and delivery table, fear of an unusual event occurring during labor such as sudden bleeding, impending cesarean section, presence of heart disease or Rh factor not understood, precipitate labor, and fear of the attending physician's not being present for the delivery—all factors which should be considered in an attempt to reduce to a minimum unpleasant emotional reactions during labor.

A study of the patients in the unsatisfactory Classes is revealing. Practically always in Class IV patients, and almost always in those in Class III, something besides ignorance of the labor process, fear of pain, and of abnormal or injured baby was found. There were sixty patients in this group. Twelve had had an immediately previous labor complicated by hemorrhage, abnormal fetal position, or some other complication, and fear for self was exaggerated in the following labor; ten had a definite history of long-standing emotional instability and insecurity; five had had recent deaths in the immediate family; four were overwhelmed by tense, and overanxious visitors; three were in the throes of marital difficulties; three had definite psychosexual problems with resulting guilt feelings; two patients definitely rejected the pregnancy and infant; and one had a religious conflict. Two-thirds of the patients having unsatisfactory labors had severe emotional conflicts and it is doubtful that reassurance alone, indoctrination, or relaxation methods would have changed the type of labor. This fact substantiates the impression that while there is organic cause for the pain of childbirth, excessive discomfort in labor is due to the emotional component of the experience.

### Comment

An accurate evaluation of emotional reactions during labor is difficult. In the first place, an objective approach requires interpretation by an observer, and it is impossible for one individual to interpret exactly another's sensations and emotions. Objectivity is also difficult because the physician and attendants are involved in the emotional experience. On the other hand, an evaluation which comes from the patient is subjective and since she is motivated more by the unconscious than the conscious, she frequently does not know why she feels, thinks, or behaves as she does. Also, women in labor are so emotionally overwhelmed that their perception is weakened and interpretation of the situation during labor is often distorted. Post partum, she tends to remember only the pleasant and to forget the unpleasant. Because the variables are as numerous as the patients and the attendants, evaluation of the emotional reactions during labor is difficult.<sup>7</sup>

Keeping the difficulties in mind, it is felt that this study shows that as fear, anxiety, lack of knowledge of the labor process and procedures increase, the emotional reactions and pain become increasingly disturbing and unpleasant. This finding correlates with Read, and Goodrich and Thoms. The latter authors describe a well-planned course of instruction and indoctrination with emphasis on knowledge and relaxation designed to prepare the patient for her part in the labor process. There is no question of the value of this approach. However, the fact cannot be ignored that 88 per cent of the patients in the present study without special training had satisfactory labors. It is probable that these women would be satisfied regardless of the approach to labor, providing they received adequate physical care. This does not relieve the obstetrician from his responsibility to understand the emotional reactions of his patient. Rather he should be more alert to recognize the factors contributing to satisfactory labors and conduct such labors more frequently.

In order to understand more fully the emotional component of labor, we must look beyond the factors consciously listed by the patient as fear and anxiety producing. The basic fear of death is the first and most powerful of these unconscious forces. Helene Deutsch states a psychiatric truth more or less forgotten by those who feel that all fear can be eliminated by training when she says, "In all women—the happy and the disappointed, the strong and the weak, the loving and the hating—the doubts, restlessness, impatience, and

joyful expectation all conceal the fear of delivery . . . all these fears are only provocations or intensifications of a deep hereditary fear of death."

A second often unrecognized factor contributing to the emotional reactions of a woman in labor is the identification with the fetus that has developed during the pregnancy. Frequently the mother develops a deep, strong feeling that the infant is part of her body and as separation become imminent, she develops the anxiety and fear that accompany impending body or organ loss. Emotional identification with the developing fetus also makes it possible for the mother who tends toward introversion to withdraw even more completely within herself. The impending loss of this pleasant narcissistic situation unconsciously produces the tension and conflict. These unconscious conflicts account for the frequently heard statement, "I'm not as happy now that he is here as I was before he was born."

Long-forgotten, painful emotional experiences which occurred at crucial periods in the development of the individual may unconsciously produce unpleasant emotional reactions during labor. One of these periods is the bowel and bladder training period. The painful emotions manifested when bowel and bladder training is forced too early and before the child's nervous system is sufficiently developed for conscious control, and those shown in the insecurity producing enuresis for which there has been much threatening and punishing, are buried deep in the unconscious. As this patient reaches the second stage of labor and as she feels the involuntary stimulation to bear down upon her rectum, or as the membranes rupture suddenly and she feels a gush of fluid, the childhood fears and tensions are stirred and she cries in distress, "I need to go to the toilet. I'm going to make a mess! Oh, why won't you let me go!" Her muscles tighten, she holds back as the uterine contractions occur and she becomes a patient experiencing an unsatisfactory labor.

The relationship of the patient to her mother is behind many of the unconscious fear and guilt feelings which are expressed during labor. In all the emotional development toward femininity and motherhood, identification with the mother is the source of strength. When, because of unhappy environmental situations, daughter rejection, hostility, or other factors which make it impossible for the growing child to strengthen her own personality and emotional patterns by identification with the mother, she is unprepared basically to accept the crowning experience of womanhood—childbirth. For her, the entire process is unpleasant, filled with painful emotions and sensations, and she has an unsatisfactory labor.

In the same manner, the mass of unconscious material composing the psychosexual nature of the woman contributes toward her acceptance or rejection of the labor experience. A girl who received no instruction concerning the menarche, or who rejected the instruction offered, one who is filled with guilt feelings concerning sexual experiences, will also have unpleasant emotional sensations as the body and psyche focus upon childbirth. In short, the total personality, whether basically masculine or feminine, active or passive, determines the pattern of the emotional reactions during labor.

Training and indoctrination will contribute toward better understanding and acceptance of labor by patients already within the satisfactory group, and place more patients from Class II into Class I, but deeper psychiatric understanding and psychotherapy are indicated in the remaining patients. An awareness on the part of the obstetrician of these unconscious factors should make it possible to help a patient more fully to understand herself and to bring more and more unconscious material into consciousness where teaching and indoctrination are effective.



### Summary and Conclusions

1. Emotional reactions during labor are an important part of the childbirth experience.

2. An adequate evaluation of the emotional reactions during labor is difficult because of the complex objective, subjective, conscious, and unconscious factors which must be considered. There is a need for more study of the problem.

3. A criteria for an evaluation of labor is presented and the results of a study of 500 patients to whom the criteria was applied are reported.

4. The study indicates that:

a. Approximately 85 per cent of women will have satisfactory labors providing adequate physical care is given.

b. As fear and anxiety increase, unpleasant emotional and physical sensations and the number of unsatisfactory labors increase.

c. There is organic cause for the pain of childbirth but excessive discomfort and unpleasant emotional reactions during labor are frequently due to additional emotional conflicts. These conflicts often are in the unconscious area of the personality.

d. Training, education, and indoctrination will be of benefit to those patients already well motivated for childbirth but who lack knowledge of what to expect, but will have little effect on those with more severe emotional conflicts and upon unconscious motivating factors.

5. Factors consciously contributing to satisfactory and unsatisfactory labors are listed and discussed.

6. Unconscious motivating factors and the total personality make-up which contribute to the emotional reactions during labor are briefly discussed.

7. An awareness of the emotional reactions during labor will result in more personal attention to the woman in childbirth. This will:

a. Give constant, sympathetic, reassuring care which will minimize the basic fear of death which is always present.

b. Develop fuller understanding of usually unconscious motivating factors and conflicts. This will bring them into consciousness where training, indoctrination, and education will be more effective in reducing their unfavorable effect upon the labor experience.

The author wishes to thank Dr. V. L. Ward, under whose guidance this study was carried out, and Dr. E. G. Holmstrom, for their suggestions and assistance in the preparation of this paper.

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## INJURY TO THE URINARY TRACT AS A COMPLICATION OF GYNECOLOGICAL SURGERY\*

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UNTIL recent years, injuries to the urinary tract were encountered much more frequently as an obstetrical than a gynecological complication. Modern obstetrical teaching has virtually eliminated these lesions from the obstetrical field, and at the present time the great majority of injuries to the bladder and ureter are caused by gynecological procedures. Within the past fifteen years, the operation of supravaginal hysterectomy, formerly so popular, has been largely abandoned except in cases where the cervix can be removed only with difficulty, or where great haste is necessary. In its place vaginal hysterectomy and complete abdominal hysterectomy have been substituted. In both of these procedures the dissection is necessarily quite close to the bladder and ureters, and the possibility of injury to these structures is considerable.

Recently, several such injuries were encountered in a relatively short period. For this reason it seemed timely to review our experience with urinary tract injuries, to summarize their management, and to indicate the results. Accordingly, the gynecological files for the past seven years were studied. During this time 4,491 gynecological operations were performed. Among these procedures injury to the urinary tract occurred thirty-one times. Of these, twenty-two were bladder injuries, and nine were injuries to the ureter.

TABLE I. BLADDER INJURIES

<i>Recognized With Immediate Repair.—</i>	
Vaginal hysterectomy	3
Complete abdominal hysterectomy	6
Supravaginal hysterectomy	4
Ovarian cyst	1
Ectopic pregnancy	1
	<hr/> 15
<i>Unrecognized.—</i>	
Vaginal hysterectomy	2
Complete abdominal hysterectomy	2
Supravaginal hysterectomy	2
Ovarian cyst	1
	<hr/> 7

### Bladder Injuries

Injuries to the bladder, whether recognized or unrecognized at the time of operation, occurred with about equal frequency in total, subtotal, and vaginal hysterectomies. Most bladder injuries occur during its mobilization from the

\*Presented before a regular meeting of the Chicago Gynecological Society, May 20, 1949.

body of the uterus and cervix, especially when the bladder is distorted by tumors or adherent from inflammatory processes or previous operations.

Vesical fistulas may follow an incised wound made during the course of the operation, pressure necrosis following clamping with forceps or pressure of retractors, or a suture which has caught the bladder wall, which may cut through, leaving an opening, and finally, by infection with formation of an abscess, open into the bladder.

There were twenty-two bladder injuries. Fifteen were recognized at the time of operation with immediate repair. Three were in vaginal hysterectomies, six in complete abdominal, and four in supravaginal, one during the removal of an ovarian cyst and one in a tubal pregnancy.

TABLE II. BLADDER INJURIES RECOGNIZED AT OPERATION

OPERATION	NO. CASES	AVERAGE NO. DAYS IN HOSPITAL	AVERAGE NO. DAYS MORBID	COURSE
Vaginal hysterectomy	3	10	2	Uneventful
Complete abdominal hysterectomy	6	12	2	Uneventful
Supravaginal hysterectomy	4	11	1	Uneventful
Oophorectomy	1	10	0	Uneventful
Ectopic pregnancy	1	9	1	Uneventful

Of the recognized bladder injuries during subtotal hysterectomy, one was for fibromyomas with sarcomatous degeneration, one for menorrhagia with retrodisplacement of the uterus with associated pelvic inflammatory disease, and two for uncomplicated fibromyomas.

In the total abdominal hysterectomy group, one was for adenomyosis and endometriosis, one for fibromyomas and endometriosis, and two for fibromyomas with pelvic inflammatory residues. In the vaginal hysterectomy group, one was for uterine prolapse, one for fibromyomas not requiring morecellation, and one intraligamentary fibromyoma requiring morecellation. The oophorectomy was done for an adherent serous cystoma.

If the injury is recognized at the time of operation and immediately repaired and the bladder put at rest with an indwelling catheter, postoperative complications rarely result. In this group the average stay in the hospital was approximately eleven days. The average number of days of morbidity was one and a fraction and all patients had uneventful recoveries.

In seven cases the bladder injury was not recognized at the time of operation. Of this group, two occurred in vaginal hysterectomies, two occurred in complete abdominal hysterectomies, two in supravaginal hysterectomies, and one during removal of an adherent simple cystoma of the ovary. The hospital course is summarized in Table III.

TABLE III. BLADDER INJURIES NOT RECOGNIZED AT OPERATION

OPERATION	NO. CASES	AVERAGE NO. DAYS IN HOSPITAL	AVERAGE NO. DAYS MORBID	COURSE
Vaginal hysterectomy	2	44	16	Stormy
Complete abdominal hysterectomy	2	21	11	Stormy
Supravaginal hysterectomy	2	22	10	Stormy
Oophorectomy	1	24	9	Stormy

In all cases in which the bladder injury was not recognized immediately, the postoperative course was stormy. Of the two patients who had vaginal hysterectomies, one had a vesicovaginal fistula in which leakage began on the ninth

postoperative days; on the nineteenth postoperative day the fistula was electrocoagulated transurethrally, and has not recurred. The other patient promptly developed a generalized peritonitis, due to extravasation of urine into the abdominal cavity. A transperitoneal repair of the fistula was attempted thirty-six hours postoperatively, and the abdominal cavity drained. An abdominal urinary fistula resulted, which was successfully closed four weeks later. In the complete abdominal hysterectomy group, one patient developed a urinary fistula through the abdominal incision, this appearing on the seventh postoperative day. Secondary closure was done on the tenth postoperative day and was successful. The other patient developed a vesicovaginal fistula on the ninth postoperative day. This closed spontaneously on the twenty-eighth postoperative day. Of the patients with supravaginal hysterectomies, one developed symptoms of peritonitis with resulting abdominal fistula; this healed spontaneously in three weeks with the aid of an indwelling catheter in the bladder. The second had an abdominal fistula which required secondary abdominal closure six weeks later. The oophorectomy was performed for an adherent serous cystoma with resulting abdominal vesical fistula; secondary abdominal closure was successful three months later.

In the unrecognized cases the average stay in hospital was thirty days, as compared to eleven days for recognized cases. The average number of days of morbidity was fourteen compared to one plus days in the recognized group. The convalescence was stormy in all the unrecognized cases.

### Ureteral Injuries

Injuries of the ureters are more serious than those of the bladder; particularly so because many of them are not recognized during the operative procedure. Of the nine ureteral injuries in this series only two were recognized at the time of operation.

TABLE IV. URETERAL INJURIES

<i>Recognized.</i> —	
Vaginal hysterectomy	0
Complete abdominal hysterectomy	1
Supravaginal hysterectomy	1
Other operations	0
<i>Unrecognized.</i> —	
Vaginal hysterectomy	1
Complete abdominal hysterectomy	5
Supravaginal hysterectomy	0
Other operations (ovarian cyst)	1

Complete abdominal hysterectomy with removal of intraligamentous tumors is the procedure in which ureteral injury is most likely to occur. This injury may take place in a number of ways; e.g., the ureter may be clamped, cut, ligated, or traumatized. When extensive exposure of the ureter is necessary, its blood and nerve supply may be interfered with. The most frequent site of injury to the ureter, particularly in complete abdominal hysterectomy, is that portion just lateral to and below the uterine artery, i.e., 1.5 cm. from the cervix at the level of the internal os and 1 cm. from the cervix at the vaginal reflection. The next most common site is the point at which the ureter passes over the brim of the pelvis. Two of the cases were in this area. During the removal of large intraligamentous tumors the ureter may be injured at almost any point. As many of these injuries are not recognized at the time of operation, the fact that the ureter has been damaged may not be immediately apparent. Undoubtedly, there have been many injuries which produced no symptoms and were never recognized.



In the entire series of 4,491 operations, there were ten unilateral injuries to the ureters. Only two were recognized at the time of operation, one each with a total and a subtotal hysterectomy. There were none after either vaginal hysterectomies or other types of gynecological operations.

One of the recognized injuries was a severed ureter which was ligated with catgut. Due to subsequent pyonephrosis, nephrectomy was necessary. The other was one in which the ureter was ligated, and this was recognized during peritonization. The ligature was removed and a ureteral catheter was inserted immediately after operation and allowed to remain in place for two weeks. The patient had an uneventful recovery and has remained well. Both of these patients had uncomplicated postoperative courses.

Unrecognized ureteral injuries present a very different problem. There were five unrecognized injuries during complete abdominal hysterectomies, none in subtotal, and one during a vaginal hysterectomy. In the patients with total abdominal hysterectomies the average stay in the hospital was twenty-one plus days with an average morbidity of nine days.

TABLE V. UNRECOGNIZED URETERAL INJURIES

OPERATION	NO. CASES	DAYS IN HOSPITAL	MORBID DAYS	COURSE
Total hysterectomy	Case No. 1	26	11	Stormy
	Case No. 2	24	14	Stormy
	Case No. 3	30	12	Stormy
	Case No. 4	14	2	Stormy
	Case No. 5	14	4	Stormy
Vaginal hysterectomy, ureteral vaginal fistula	1	10	3	Uneventful in hospital
Oophorectomy, ureteral abdominal fistula	1	34	22	Stormy

Of the five total abdominal hysterectomies, ureterovaginal fistula occurred in all. One was following extensive endometriosis. Symptoms of vaginal urinary leakage appeared on the third day. Ureterocystostomy was done on the fifth day with excellent result. One followed fibromyomas and extensive pelvic inflammatory disease. Spontaneous closure occurred in six weeks because of nonfunctioning kidney. One followed fibromyomas and endometriosis with pyonephrosis resulting from the ureteral injury. Nephrectomy was performed three weeks later. One operation was done for an intraligamentary fibromyoma and endometriosis; the fistula is still draining four months postoperatively. The fifth followed a laparotomy for extensive endometriosis and fibromyomas; spontaneous closure occurred after eight weeks from nonfunctioning kidney.

In the vaginal hysterectomy case, performed for simple fibromyomas, the hospital stay was uncomplicated but the patient developed a ureterovaginal fistula six weeks after operation. Eventually it healed because of nonfunctioning kidney.

One unrecognized ureteral injury occurred during the removal of an adherent intraligamentary ovarian cyst subsequent to a previous vaginal hysterectomy. There was some question at the time whether the ureter might have been injured by a clamp. Urinary leakage occurred and signs of peritonitis appeared. An abdominal abscess was drained on the fourteenth day and an abdominal fistula remained or followed. This patient was in the hospital for twenty-two days. She re-entered for a nephrectomy because of a persistent uretero-abdominal fistula. Three months later an abdominal abscess was drained. Four months later she re-entered the hospital because of abdominal wall sinus from which a piece of black silk was removed.

In nearly all of the urinary injuries in this series in which hysterectomy was done, either abdominal or vaginal, the anatomical distortion due to the associated pathology was probably responsible for the accidents rather than the hysterectomy itself. The most frequent associated pathology is endometriosis, adhesions from pelvic inflammatory disease and from previous operations, intraligamentary tumors, cervical and low-lying uterine fibroids, all of which may cause distortion of bladder and ureters.

### Comment

Injury to the urethra, bladder, and ureter continues to disturb the gynecological surgeon because of its frequency as a complication of pelvic operations. Because of the seriousness of urinary tract injury, every effort should be made to avoid this complication, and if this is not possible, to recognize it at once.

The injection of 5 to 10 c.c. of methylene blue into the bladder following preoperative catheterization aids greatly in immediate perception of bladder injury. An opening in the bladder is immediately apparent, and even if the bladder wall is not completely cut through, the blue color may be seen through the mucosa. This simple and harmless procedure is extremely useful. Two of the bladder injuries included in this series occurred upon opening the anterior abdominal wall. It would seem proper to urge that in all cases, and particularly those in which the relations may be distorted by previous operations, the peritoneal cavity be entered near the upper angle of the abdominal incision, for here there is much less likelihood of encountering an advanced bladder.

Properly dissecting the bladder from the anterior wall of the uterus and retracting downward and forward may increase the distance of the ureter from the cervix.

During vaginal hysterectomy the bladder should at all times be retracted upward and anteriorly, thereby carrying the ureters with it. It is also of the greatest importance that all clamps and ligatures be placed as closely as possible to the body of the uterus.

Intraligamentary tumors should be removed by blunt dissection, with great care not to tear through or incise any apparent band of adhesions without carefully determining its nature.

If the operator expects to encounter fixation of the pelvic organs because of extensive inflammatory disease, endometriosis, intraligamentary tumors, or extensive adhesions following pelvic surgery, catheters should be passed into both ureters prior to operation. If the ureters are encountered unexpectedly, catheters may be inserted at any stage of the operation. If these simple measures are followed the majority of urinary tract injuries will be prevented; and most of those which do occur will be immediately recognized.

### Treatment

#### *A. Recognized Injuries.—*

Bladder injuries which are recognized at the time of operation should be immediately closed with fine catgut. Two layers of sutures should be employed, the most superficial of which should be an inverting suture. If the edges of the defect are devitalized, these should be excised irrespective of their extent, and the fresh edges approximated. These injuries ordinarily heal without incident, even though a significant portion of the bladder is amputated. An indwelling catheter should be inserted at the close of the operation, and this is best irrigated gently with dilute boric acid solution twice daily to insure its remaining open. Also, the urine should be kept sterile with some form of urinary antiseptic. The catheter may be removed in eight to ten days, and uneventful recovery should be expected.

If the ureter is severed and this is recognized at the time, management will depend on the level at which it is divided and the condition of the other kidney. If the condition of the other kidney is not known, the proximal end of the ureter may be brought out through a puncture wound in the abdominal wall until the condition of the other kidney is determined.

If the ureter is cut at a point which will permit the implantation of the end of the ureter into the bladder without tension, ureterocystostomy is a satisfactory manner in which to deal with it. The lower portion of the ureter should then be ligated.

Ureteral anastomosis may be attempted by splinting the ureter with a ureteral catheter. This is threaded through the ureteral defect, one end extending into the bladder and the other toward the pelvis of the kidney; the bladder end is later brought out through the urethra. The cut ends of the ureter can then be united with very fine catgut sutures. Some authorities advise that a second catheter be passed higher than the first in order that the urine may be shunted around the defective area. One must be sure that peritonization is complete in order to prevent any urinary leakage into the peritoneal cavity. Nephrostomy is rarely necessary, but may be kept in mind as a means of temporarily preserving kidney function if immediate repair of the ureteral defect is not possible.

The catheters should be allowed to remain in place for from ten days to two weeks before removal.

If the division of the ureter took place at a level which renders implantation into bladder impossible or the condition of the patient is such that it would be unwise to lengthen the operation further by a time-consuming anastomosis, the proximal end of the ureter may be brought out through a stab wound in the abdominal wall and allowed to drain until the condition of the patient permits some other method of dealing with the situation; or the cut ends of the ureter may be ligated, preferably with nonabsorbable material. Absorbable material may give way with formation of an abscess or ureterocervical or ureterovaginal fistula.

Ureterointestinal anastomosis may be done but this method of dealing with an incised ureter is not well thought of by most authorities.

Ligation of the ureter results in ultimate atrophy of the kidney. The sudden and complete stoppage of urinary flow from the kidney is much more likely to cause cessation of renal function than a slower or partial obstruction, which usually causes hydronephrosis. The operator should be sure of the presence of the other kidney before resorting to ligation.

When the ureter is tied and this is discovered before the close of the operation, the ligature should immediately be removed. After the operation a ureteral catheter may be inserted and left in for seven to ten days. This usually results in a normally functioning ureter. This also should be done if the ureter has been accidentally clamped.

#### *B. Unrecognized Injuries.—*

When the injury to the urinary tract is such that urinary extravasation occurs into the tissues, the condition must be dealt with upon its own merits. As the first step in determining the site of such an injury, cystoscopy and ureteral catheterization are of the greatest importance. Bladder defects may occasionally be dealt with upon this basis alone; ureteral injuries may be localized as a guide to repair.

When urinary leakage through the vagina is the first sign of injury to the urinary tract, one must determine promptly whether this leakage is of vesical or ureteral origin. This differentiation between vesicovaginal and ureterovaginal fistula is easily made by the instillation of methylene blue into

the bladder, or by retrograde pyelography. In the former case spontaneous closure is the rule; ureterovaginal fistula, in our experience, may heal spontaneously because of ultimate non-functioning of the kidney. For this reason it is recommended that once the diagnosis of ureterovaginal fistula is made a complete urologic study should be made promptly in order to determine the best means of preserving function of the affected kidney.

TABLE VI. INJURIES TO BLADDER AND URETER IN HYSTERECTOMY

OPERATION	NO. CASES	TOTAL INJURIES		BLADDER		URETER	
		NO.	%	NO.	%	NO.	%
Complete abdominal	808	14	1.73	8	0.99	6	0.74
Supravaginal	484	7	1.45	6	1.24	1	0.23
Vaginal	328	6	1.83	5	1.52	1	0.32
Total incidence of injury in all hysterectomies (27 of 1,620 cases)						1.67%	

### Summary and Conclusions

In the past seven years, 4,491 gynecological operations were performed at the Evanston Hospital. Among these procedures, thirty-one patients sustained injuries to the urinary tract. The details of these injuries are presented.

In all cases in which the injuries were recognized at the time of operation, and were capable of being repaired, the postoperative course was uneventful. In all cases in which the injury was unrecognized at the time of operation, the postoperative course was extremely stormy. The ordinary means by which these injuries may be prevented is mentioned. It is particularly urged (a) that methylene blue be instilled into the bladder before all major gynecological procedures as an aid to the immediate recognition of bladder injuries, and (b) that catheters be placed in the ureters prior to any gynecological procedure in which extensive adhesions or difficult dissections are anticipated. It is considered that by these means the great majority of urinary tract injuries will be either prevented altogether or rendered immediately recognizable.

Since some vesicovaginal fistulas heal spontaneously, it is considered proper that these be observed for a prolonged period before repair is attempted.

Since ureterovaginal fistulas so frequently heal as the result of nonfunction of the affected kidney, it is urged that these lesions be dealt with immediately upon recognition.

414 CHURCH STREET.

### Discussion

DR. FRED O. PRIEST.—At the Presbyterian Hospital we have instilled 10 c.c. of indigo carmine solution into the empty bladder preceding all pelvic surgery except dilatation and curettage. The importance of immediate recognition of the damage and repair at once cannot be overemphasized. Keeping the bladder at rest demands excellent nursing care. Distention of the bladder wall, particularly at about the time of catgut absorption, may break down a perfectly repaired laceration. Our results with closure of recognized bladder injuries are not as good as Dr. Holloway's.

In reviewing the gynecological records at Presbyterian Hospital from January, 1939, to April, 1949, we recognized damage to the bladder or urethra at the time of surgery on sixteen patients. Four of these were during total abdominal hysterectomy, though two of them had nothing to do with the technique of the hysterectomy itself. The bladder



was opened once upon entering the peritoneum, and lacerated by the needle once during peritonization. Both were promptly repaired and healed. Twice the bladder was opened and this was recognized during the actual technique of total abdominal hysterectomy proper. One of these healed primarily, the other after four attempts at secondary repair. Seven times bladder injury was recognized during vaginal hysterectomy, none of which were morcellation operations; four of them healed primarily; two had pin-point openings left and were treated by radium needle therapy (100 mg. hr.), and one healed after secondary closure. Three times the urethral bulb or bladder has been opened during performance of anterior plastic. Each healed primarily. The hospital stay in these recognized cases was comparable to that in Dr. Holloway's series.

As to the unrecognized damage, five times it occurred after vaginal hysterectomy. Loss of urine appeared from eight to fifteen days postoperatively; one injury healed spontaneously; three healed at the first attempt at closure; one required two closures.

Two ureterovaginal fistulas have followed unrecognized damage in total abdominal hysterectomy. One was cured by atrophy of the kidney. Nephrectomy was done in the second case because of pyelonephrosis. One ureterovaginal fistula followed removal of the cervical stump. Nephrectomy was done after study. The patient had a stormy convalescence.

In addition to the above positive cases, six times the urine has been found to contain blood following vaginal hysterectomy. All were treated by retention catheter, urinary antiseptics, etc. None developed fistula though there may have been minute lacerations or needle trauma in the surgical technique.

Dr. Holloway has pointed out that the most likely time for bladder injury is in freeing it from the fundus and upper cervix. Some of these injuries may be avoided in vaginal hysterectomy, if we will decrease our determination to open the anterior cul-de-sac when difficulty is encountered. The bladder and ureters may be retracted forward well even though we have not opened the anterior peritoneum. After freeing the sacrouterine ligaments and the bases of the broad ligaments the anterior peritoneum may be exposed quite easily. If it is not, however, the technique may be continued until the fundus can be tipped backward, a finger passed behind it, and the peritoneal reflection located accurately. Morcellation technique may be carried out posteriorly if the anterior cul-de-sac cannot be entered.

The fistulas which appear eight days and later following vaginal hysterectomies are probably due to crushing bladder tissue or catching it in the suture while closing. One of my own cases followed a very easy vaginal hysterectomy. The patient had been completely dry for ten days, without a retention catheter, and at no time had she had blood in the urine. The fistula was located in the center of the vaginal vault incision. In the future I shall be less persistent in obliterating the dead space between the bladder and the anterior vaginal mucosa.

DR. VINCENT J. O'CONOR (by invitation).—At the Evanston Hospital there was a percentage of 1.67 in which some sort of damage occurred to the ureter or to the bladder during extensive pelvic surgery. The Evanston Hospital is in a community where most people go for medical attention without waiting too long, so perhaps the complications of such surgery there are not as great as they might be, for instance, in the County Hospital. I feel that a group of this kind should be told, as I wish someone would come before the urological group and do likewise, that no one should be ashamed to have such a minimum percentage of these complications occur.

Recently, in discussing the subject of vesicovaginal fistula I made a statement which I now wish to retract: that with the advent of more universal vaginal hysterectomy, bladder injuries had become more common. This is not the truth as far as our own records are concerned. We have had at the Wesley Memorial Hospital during its present life twelve ureterovaginal fistulas, simple, and twenty-two vesicovaginal fistulas, six of which were complicated by ureterovaginal fistulas. I would like to stress that uretero-

vaginal fistula and vesicovaginal fistula are frequently associated and one must not jump to conclusion of a single opening until the patient has been carefully studied. Faulty diagnosis has caused discouragement to a rather unfortunate percentage of patients in whom the gynecologist, by seeing the vesicovaginal fistula or proving its presence by various dye injections has tried to repair it without studying the urinary tract as a whole. In several instances the patient was cured of the bladder fistula only to have continued leakage from one of the ureters.

I have seen in the last ten years five women who leaked urine and who had to wear pads constantly, who were told that their incontinence was due to lack of sphincter control. Some sort of sphincter tightening operation was done but the patient continued to leak urine. Another condition to be ruled out is the neurogenic bladder, both the pre-ataxic and the ataxic stages. Urinary incontinence is one condition that the urologist and gynecologist should team up on.

As Dr. Holloway has emphasized in his paper, there is a marked tendency to spontaneous healing of the bladder wall. The fistula may close with catheter drainage, with or without the assistance of destruction of the epithelial tract. We have had nineteen cases which closed with coagulation and catheter drainage. Of these nineteen, twelve patients had been operated on from one to seven times unsuccessfully. We had nine patients who were treated with coagulation and drainage, some on several occasions, but did not heal. So, before doing radical vaginal or suprapubic surgery in these fistulas, consider the possibilities of their healing by methods other than extensive surgery. Every time a vesicovaginal fistula is operated upon unsuccessfully it makes subsequent operative procedures much more difficult. In our particular hospital, of the thirty-four patients who had these accidents, all but eight of the fistulas were incurred elsewhere.

There are certain principles about the repair of vesicovaginal fistula that ought to be emphasized. One is that, when a patient has had a vaginal operation, especially a vaginal hysterectomy, vaginal closure may be considerably more difficult than in the type of fistula that we saw secondary to obstetrical injuries or to injuries secondary to pelvic repair, etc. In many of the former only a suprapubic repair will be successful. Here again gynecologists and urologists should team up. In recent years on the urological service in Wesley Memorial Hospital there were eleven patients who had had numerous unsuccessful vaginal operations for closure of vesicovaginal fistula. Nine of these were closed by suprapubic operation of a type which is rather radical but nevertheless successful. There are two ways of closing a fistula suprapubically: one is by closing the fistula within the bladder, pulling up the fistulous tract within the bladder and attempting to close it in some manner from the inside, and moving over the floor of the trigone to the wall of the bladder and closure of the area from the vaginal opening. In many instances this operation is a failure because it is impossible working through the bladder itself to get sufficient tissue to unite the opening. In that type of patient, the results are good, if you will take time to extraperitonealize the bladder wall down to the fistula, then cut the bladder practically in two down to the center of the trigone, dissect the bladder away from the fistula to the floor, close the fistula with mattress or purse-string suture, though I do not believe this is really necessary, and then close the bladder wall from the posterior side away from the fistula. This is an extensive operation which means watching the ureteral orifice carefully. We either put catheters in or inject indigo carmine so as to see the dye coming out of each orifice while we are operating. This is a most satisfactory operation for any patient who has been operated on many times unsuccessfully vaginally.

In treating vesicovaginal fistulas, the first consideration is more frequent suprapubic drainage. Most men, following Marion Sims, put in a urethral catheter. A urethral catheter is just as vulnerable as any other drainage tube and many break down because the urethral drainage becomes obstructed and pressure is put on the suture line. It is a simple matter to put additional suprapubic drainage in these patients.

Now the question is, how to prevent these accidents. Will putting colored fluid in the bladder prevent it and make early recognition possible? If so, it certainly should be

routine. Do catheters in the ureters help you to prevent these accidents? If so, then certainly this should be relatively a routine proposition. I do not believe that, with modern antibiotics and fluid balances, putting the catheters up the ureters is a particularly upsetting procedure to the patient.

I agree with Dr. Holloway that vesicovaginal fistulas should be watched and given a chance to heal. Give them postural drainage and coagulate the tract. In ureterovaginal fistulas if you cannot get a catheter up that ureter give consideration to ureteral surgery, implantation of the ureter into the bladder. Of the nineteen cases, we had two in which the condition of the kidney made it impossible to fix the ureter into the bladder and maintain a good urinary tree on that side. We had two in which the ureteral fistulas healed spontaneously with catheter drainage.

DR. IRVING J. SHAPIRO.—With the cooperation of the gynecological department at Michael Reese Hospital, I have seen a moderate number of operative injuries to the urinary tract. The urologist as a rule does not see bladder injuries as these are recognized and repaired immediately at the time of the surgery. In 1938 Dr. Leventhal and I collected the ureteral injuries that had occurred at Michael Reese Hospital in the previous fifteen years and found fourteen. Most of them had occurred in service cases in which the residents and interns had done the major portion of the surgery.

It would be very fine if Dr. Holloway's injunction to recognize these injuries at the operating table and repair them immediately could be followed. Unfortunately the great majority are not recognized, and the symptoms appear at various times in the post-operative period. Many of the lesions that appear late are due to the devitalization of the ureter from too extensive dissection rather than actual cutting.

In bilateral injuries to the ureter immediate bilateral nephrostomy must be done as a lifesaving measure. Waiting accomplishes nothing except to place the life of the patient in further jeopardy. Deligation is a hazardous procedure, and if the offending ligatures are not found, nothing has been accomplished by the operation, and the opportunity to do nephrostomy has been lost. In unilateral injury to the ureter a nephrostomy should be done to protect the kidney from dilation and infection. At a later date an attempt may be made to restore the integrity of the damaged ureter.

DR. EUGENE EDWARDS.—The bladder injury that is recognized at the time of operation is repaired and causes no further damage. The bladder injury that comes twelve, sixteen, or eighteen days after the patient leaves the hospital is one that is due to some interference with the blood supply. I cannot believe that bladder injuries should be repaired by suprapubic operation. I think they should all be closed by a vaginal procedure. As far as bladder injuries go, there is one about which nothing has been said, namely, the bladder fistula which follows radiation.

Most ureteral injuries that I have seen were located at the ovarian fossa. These may be corrected by an end-to-end anastomosis over a ureteral catheter. If this is not feasible the ureter is transplanted into the bowel or tied off. When it is necessary to ligate the ureter, it is best to dissect it out and double it on itself before ligating it.

DR. HERBERT E. SCHMITZ.—If during a pelvic laparotomy both ureters have been ligated with an absorbable ligature material, then it is best to perform a bilateral nephrostomy, permitting drainage from the kidney pelvis until such a time as the ligature absorbs and catheters can be passed up the ureters. The tube can then be withdrawn from the kidney pelvis and the nephrostomy wounds will close without any permanent damage to the kidney. I would warn against catheterizing the ureters before pelvic surgery is undertaken. Meigs has brought to our attention the fact that greater trauma is experienced when forceps come in contact with the wound of the ureter while a hard object, such as a catheter, is within the lumen. He found a 12 per cent incidence of urethral fistulas in his first reported series of Wertheim operations. These were due to the fact that the blood supply to the lower third of the urethra had not been carefully protected and he found from later experience if nothing is done these fistulas heal spontaneously.

I would like to say something about our technique of total abdominal hysterectomy. If the peritoneum is cut across at the junction of the sacrouterine ligament and the uterus, and this carefully pushed down to the floor of the pelvis, the ureters are then brought well out of the area where the clamps are applied to crush the uterine vessels. If this procedure is carried out there is very little danger of injuring the ureters.

DR. HOLLOWAY (Closing).—Dr. Shapiro must have misunderstood me; we had no cases in which both ureters were tied off. Fortunately, our cases were all unilateral.

Dr. Edwards spoke about bladder fistula following radiation. In this particular series we had none.



## THE PRINCIPAL CAUSE OF BREECH PRESENTATION IN SINGLE TERM PREGNANCIES

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FOR several centuries theories have been propounded as to why the human fetus presents by the breech in about 3 per cent of all term deliveries. Current texts list the following causes for breech presentation: prematurity, placenta previa, hydrocephalus, multiparity, multiple pregnancy, contracted pelvis, and pelvic tumors.<sup>1</sup> These are, in the main, disconnected reasons given without regard for underlying functional principles which might exert a standard influence under all circumstances. Vartan,<sup>2</sup> in 1940, in a paper on the etiology of breech presentation, wrote: "What struck me and still impresses me concerning the etiology of breech presentation is that most of these factors which are reputed to be causes seldom occur. I concluded, therefore, that either the 'cause' is so rare as to be almost a chance coincidence or that the cause in almost every case is unknown." In a second paper on this subject, in which he<sup>3</sup> outlined further considerations, he arrived at the same conclusions.

Tompkins,<sup>4</sup> in reporting a series of 911 cases of breech delivery, made a thorough analysis of all listed causes, and showed that multiple pregnancy and prematurity play definite causal roles in breech presentation. The first of these has long been recognized. The second has been established by Weisman,<sup>5</sup> in his x-ray studies of fetal presentation made periodically from about 20 weeks of pregnancy until term. Weisman demonstrated that about 24 per cent of fetuses present by breech at 18 to 22 weeks of pregnancy, and that this figure was decreased to 8 per cent by 28 to 30 weeks, and to 7 per cent by 34 weeks. We know from experience that by 38 to 40 weeks all but about 2.8 per cent of these fetuses have undergone spontaneous version to cephalic presentation.

Tompkins<sup>4</sup> found, in his study of 4,138 breech deliveries of single pregnancies, that maturity and weight of the fetus are factors. In babies weighing from 1,000 to 1,499 grams, 35 per cent were delivered as breeches. In the 1,500 to 1,999 gram group, 17 per cent were so delivered; 8 per cent of the 2,000 to 2,499 gram group were breech deliveries, and 3.5 per cent of the 2,500 to 2,999 gram group, 3.6 per cent of the 3,000 to 3,499 gram group, and 1.7 per cent of the 3,500 to 3,999 gram group were delivered as breeches. In the 4,000-and-higher gram group the percentage of breech deliveries was 2.4 per cent.

Tompkins<sup>4</sup> further showed that some women appear to possess an individual tendency to have more breech deliveries than the average expectancy would indicate. Cartledge and Hancock<sup>6</sup> studied a family in which the mother, delivered as a breech herself, had six children, all of whom were breech deliveries. Three of these were girls who subsequently bore a total of five babies. Again all delivered as breeches. This is a very unusual report, and causes one to

speculate upon the possibility of some inherited factor causing bicornate uterus in the mother and daughters. To establish or remove from consideration the reality of such coincidence additional studies are required.

Tompkins<sup>4</sup> also studied the possible etiologic role of contracted pelvis, gross fetal abnormalities, placenta previa, pelvic tumors, uterine scars, maternal obesity, and maternal age, but no definite relationship could be shown. Young<sup>7</sup> found that 26 per cent of hydrocephalic infants and 18 per cent of anencephalic ones weighing over 2,500 grams delivered as breeches. These abnormalities, thus, do predispose toward breech presentation, but in any large series their frequency of occurrence is so negligibly small that they do not play any real part in the over-all picture of breech presentation. In 35 cases of bicornate uteri reported by Smith<sup>8</sup> there were 15 breech presentations, but this uterine anomaly occurred in only 0.6 per cent of the series of cases reported by Tompkins<sup>4</sup> and thus it is only a minor cause.

In the summary of his very thorough article Tompkins<sup>4</sup> stated that he believed the cause of only about 4 per cent of term breech presentations could be accounted for, and these were on the basis of gross fetal anomalies, placenta previa, pelvic tumors, and uterine anomalies. He further stated: "For reasons by no means clear the fetus tends to assume a cephalic presentation in late pregnancy," and, admitting his bewilderment, in a lighter vein, he added: "Perhaps the fetus faces the exit for the same reason that a person in an elevator faces the exit, or vice versa."

In a recent paper by the author<sup>9</sup> on the causes of transverse or oblique presentation of the fetus in the last ten weeks of pregnancy it was shown that *the position of the placenta, in situ in the near-term or term uterus, as it indented and altered the ovoid shape of the amniotic sac, was the chief controlling factor of fetal presentation.* In about 92 per cent of the 52 cases of transverse or oblique presentation reported in that paper the placenta was either a previa or was implanted wholly or mostly in the fundus. It was also mentioned that the significance of a characteristic placental implantation position was being established in cases of breech presentation, and that a subsequent paper would contain a complete report of these findings.

### Material

In establishing the basic relationships between the placenta and the fetus we studied the soft-tissue placentography x-rays taken of 76 gravid women who had persistent breech presentation at term or in the last few weeks of pregnancy. These cases were not selected except in so far as only those patients with breech presentation who, for various reasons, had had anteroposterior and lateral x-rays of the uterus were utilized. In nearly half of the cases in our series x-ray studies were carried out as soon as breech presentation was suspected or discovered. These are the cases from the Herman Kiefer Hospital, and they thus represent a series of patients with breech presentation taken from consecutive hospital admissions. The hospital records of all of the patients in the series were analyzed for clinical findings and parity, and the data are utilized in Tables I, II, and III. In one-third of the Herman Kiefer Hospital cases the actual in situ position of the placenta in the uterus was checked against the x-ray findings by careful intrauterine palpation of the as yet unseparated placenta done immediately following delivery of the infant. In those instances in which the woman was delivered by cesarean section, similar palpation of the actual placental position in the uterus was immediately performed.

In every case the placenta was found to be implanted just as pictured in the x-ray films. All of the films were read by the author, who, in a recent paper,<sup>10</sup> showed that the placental position in the near-term or term uterus

could be accurately determined, by soft-tissue placentography x-rays, in 97.8 per cent of a series of 472 cases so studied. The common cornual placental implantation positions are shown in Fig. 1; the frequency of the occurrence of each type is shown in Table III.

THE THREE COMMON TYPES OF "CORNUAL-FUNDAL" PLACENTAL IMPLANTATION

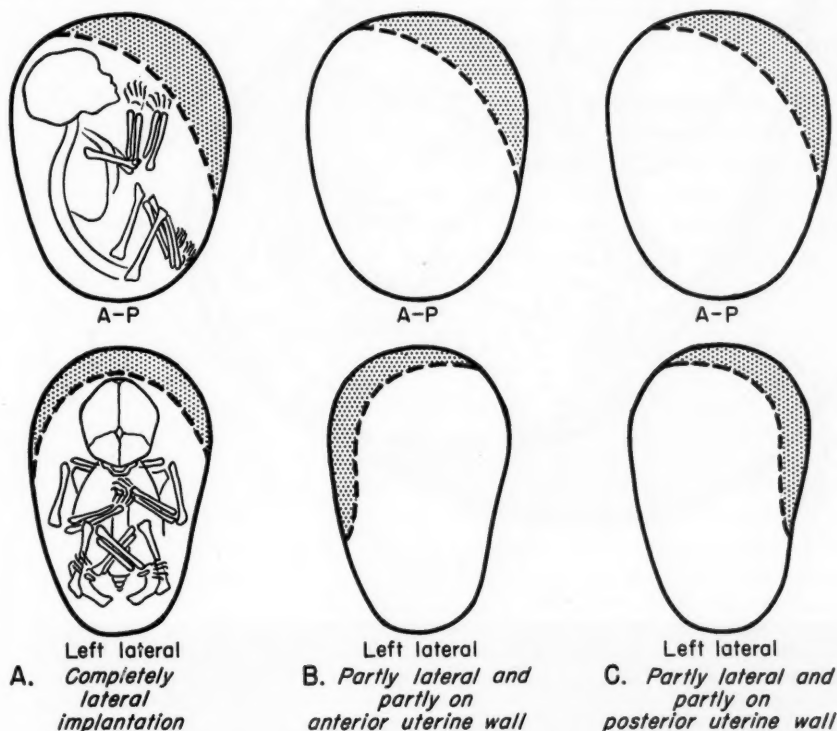


Fig. 1.—The above sketches are adapted from soft-tissue placentography x-ray films and show anteroposterior (upper row) and left lateral (lower row) views of the term uterus. The three common types of left cornual-fundal placental implantation are pictured. When the placenta is in the right cornu, the anteroposterior views would picture the mirror images of the three figures on the top row, but the lateral views would be the same.

In our series of 76 cases (Table III), 22 had right cornual implantation of the placenta and in 54 it was implanted in the left cornu. The placenta was directly lateral on the right in 6 cases and in 17 cases directly lateral on the left. It was in the right cornu but partly in the anterior fundus in 5 patients, and in the left cornu and partly anterior in 19. In 11 women the placenta was in the right cornu and partly posterior, and was in the left cornu and partly posterior in 18. Thus 23 of the placentas were directly lateral, 24 were lateral and partly anterior, and 29 were lateral and partly posterior.

In reviewing the well-known experiments of Duncan,<sup>11</sup> Veit,<sup>12</sup> Schatz,<sup>13</sup> and Seitz<sup>14</sup> on the effect of gravity upon fetal presentation, one perceives that no definite causal role for this natural force could be conclusively established. The theory of accommodation, as advanced by Dubois,<sup>15</sup> Simpson,<sup>16</sup> Scanzoni,<sup>17</sup> Pinard,<sup>18</sup> and Sellheim,<sup>19</sup> held that cephalic presentations are brought about by a process of accommodation between the fetal ovoid (the breech and legs comprising the larger fetal pole) and the interior of the uterine cavity, the shape of this cavity being such that the fetus is most comfortable and fits it most accurately and evenly when presenting by the head.

Credence to the validity of the theory of accommodation of the fetus is lent by one's experiences when routinely performing external version on fetuses presenting by the breech. Experience shows that one often must repeat such

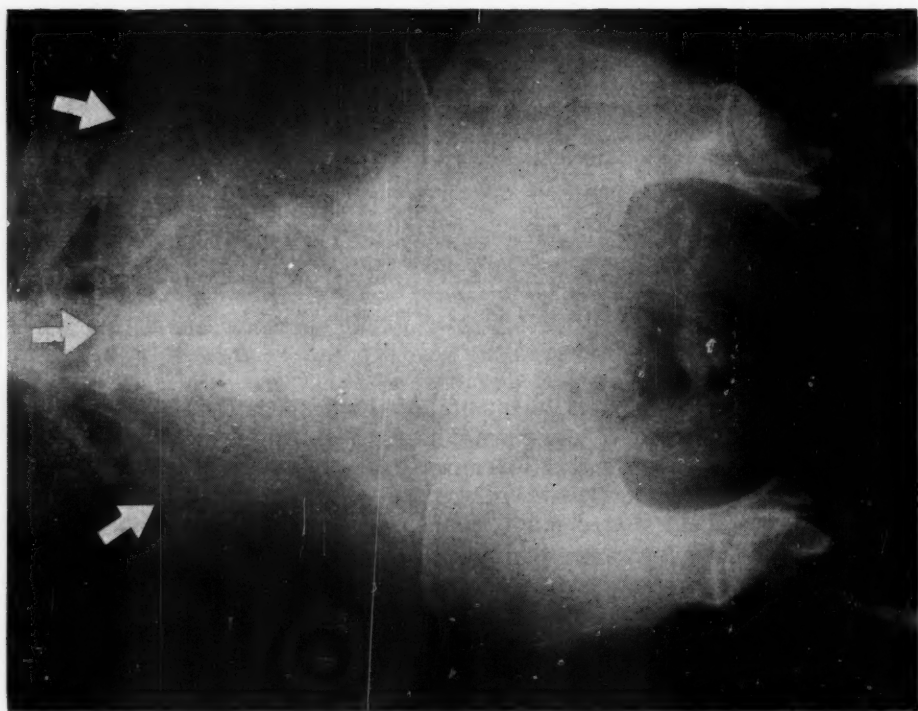
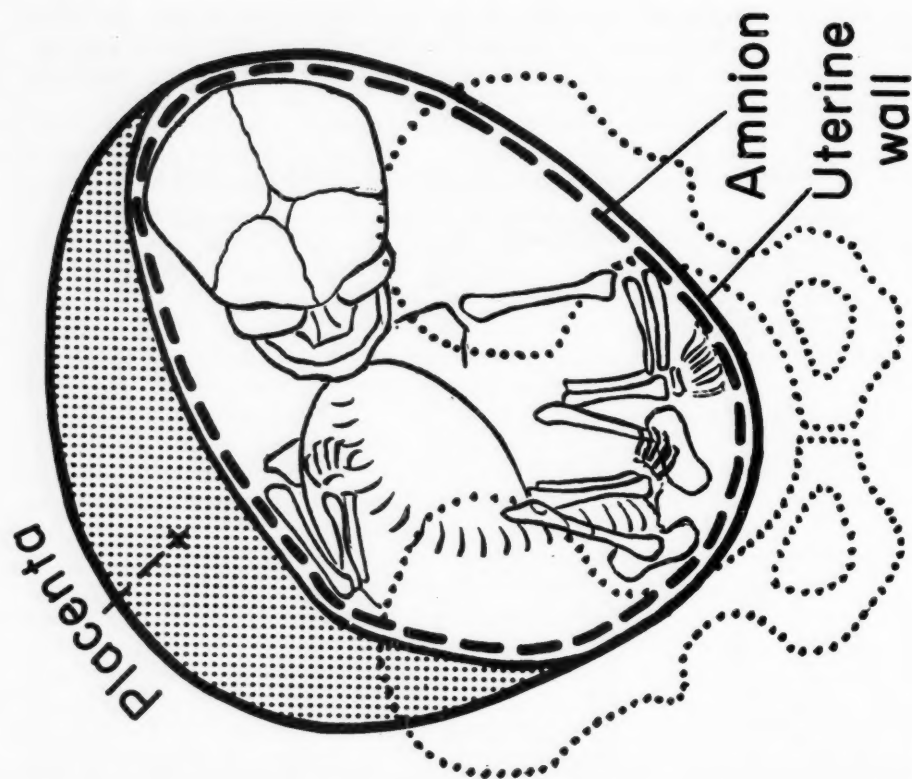


Fig. 2.—Typical anteroposterior x-ray picture in breech presentation. S. C., H.K.H. No. 103174, a 34-year-old gravida iv, para iii, three weeks from term, subsequently went into labor with the breech presentation. The placenta is seen to be implanted in the right cornual-fundal region of the uterus, as is shown in the adjoining tracing sketch made from the x-ray film and the photograph of it. In best accommodating itself to the shape of the amniotic sac the fetus has its head in the smaller of the two poles of the sac and its breech in the larger pole. Because of the position of the placenta in the uterus the polarity of the amniotic sac is independent of and different from the fixed polarity of the containing uterus.



version on the same patient and even then one may find that the fetus has again returned to breech presentation in from a few hours to about two weeks after having been externally converted to cephalic presentation. Also, on several occasions, we have mistakenly judged, by palpation alone, a fetus to be presenting by the breech, and have performed an external version upon it, erroneously converting it from cephalic to breech presentation, as proved by x-ray. And subsequently this same fetus may be found to have returned spontaneously to cephalic presentation. It was these common experiences which first caused the author to reflect upon and study the causes of the various fetal presentations.

These studies lead to the conclusion that cornual implantation of the placenta causes the fundal pole of the amniotic sac to have relatively the same size, or capacity, as, or even a smaller capacity than, the lower uterine segment pole of the sac (Fig. 2). *Since the fetal head is smaller than its breech and legs, the head will tend to accommodate itself to the smaller pole of the amniotic sac ovoid, while the breech will tend to accommodate itself in the larger lower uterine segment of the sac.* We conclude, thus, that cornual implantation of the placenta, as it indents and alters the shape of the amniotic sac (Figs. 1 and 2), is the principal cause of breech presentation of the human fetus (Table I).

The results of the soft-tissue placentographic x-ray studies on our series of cases with breech presentation are shown in Table I. The placenta was found to be principally implanted in either the right or left cornual region of the uterus in all cases upon which x-ray studies had been made. The x-rays of all but three of the 76 cases presented were taken at or within two to three weeks of term, and thus practically all fetuses that were going to undergo spontaneous version to cephalic presentation would have done so by this time. The series includes an interesting case (H.K.H. No. 101720) in which cephalic presentation was present three days prior to delivery, as determined by x-ray studies (Fig. 3), and it was predicted, because of the left cornual implantation of the placenta, that the fetus in this case had a good chance of undergoing spontaneous version to breech presentation. The patient entered the hospital in labor three days later with the breech presenting in left sacrotransverse position and was shortly delivered, by breech extraction, of a 2,870 gram infant.

It is interesting to note from Table I that 71 per cent of the patients had the placenta implanted in the left cornu, as against 29 per cent with it in the right. The 10 to 15 degree right torsion of the uterus, which is present at or near term in 80 per cent or better of all cases, seemed to us to be the most probable explanation of this finding. This aspect of the subject, including the additional effect of parity, will be further treated in subsequent paragraphs.

We have considered the possible causal factors determined by Tompkins<sup>4</sup> and analyzed our series of cases regarding them (Table II), and find that the number of patients in our series is not large enough to have allowed us to encounter in them all of the etiological factors he lists.

In considering the role played by placenta previa in breech presentation of the fetus, we reviewed the data collected on 56 cases of placenta previa<sup>20</sup> at the Boston Lying-in Hospital. We found breech presentation in four cases, in none of which did the pregnancy continue beyond 36 weeks. One instance occurred in a case of complete previa, none were found in the partial previa group, and three were found in patients with marginal previa. In this series of 56 cases of placenta previa the average duration of pregnancy was 33.7 weeks, at which time an incidence for breech presentation of 7 to 8 per cent is to be expected. It is believed that it will be difficult to find patients with breech presenta-

TABLE I. A COMPARISON OF THE GENERAL PLACENTAL IMPLANTATION SITES, EXPRESSED IN PERCENTAGE OF OCCURRENCE, IN THE NEAR-TERM UTERUS IN A SERIES OF CASES OF BRECH PRESENTATION, A SERIES WITH PERSISTENT TRANSVERSE OR OBLIQUE PRESENTATION, AND A SERIES IN WHICH THE INCIDENCES OF THE VARIOUS FETAL PRESENTATIONS WERE OF RELATIVELY NORMAL OCCURRENCE

FETAL PRESENTATIONS	MID-FUNDUS	ANTERIOR HALF OF FUNDUS	POSTERIOR HALF OF FUNDUS	RIGHT FUNDAL AND CORNUAL REGION	LEFT FUNDAL AND CORNUAL REGION	MID-ANTERIOR WALL	MID-POSTERIOR WALL	LATERAL WALL OF UTERINE BODY	LOW ANTERIOR WALL	LOW POSTERIOR WALL	PLACENTA PREVIA
Breech presentation* (76 cases)	0	0	0	29	71	0	0	0	0	0	0
Transverse or oblique presentation <sup>9</sup> (52 cases)	25.0	15.4	5.8	0	2.0	7.6	0	0	11.6	5.8	26.8
All fetal presentations of normal average occurrence† (207 cases)	7.5	Not mentioned	Not mentioned	<i>Tubercle placenta</i> 7.0		37.7	35.3	11.1	1.0	Not mentioned	0.4

\*We have thus far been unsuccessful in our search for a case of single pregnancy at or near term with a normal fetus in breech presentation in which the placenta was not implanted in one or the other cornual regions of the uterus. In going over standard obstetric texts we have found faithful reproductions of two "frozen sections" of women who had breech presentation at term and died undelivered. One,<sup>22</sup> after Waldeyer, shows the cross-sectional view of the left half of a woman's body, as viewed from the right, and a fetus is seen lying in left sacro-transverse position with its head in what must have been the right half of the fundus. The thin cross-section of the edge of the in situ placenta is wholly in the fundus (see Fig. 1, A, lateral view) and it appears to be a directly lateral left cornual implantation. The second "frozen section,"<sup>23</sup> after Williams, presents a similar view except that the woman died in the second stage of labor and the placenta is implanted partially in the posterior fundus and partially in the left cornual region (see Fig. 1, C, lateral view). These two cases are the only such we have as yet found and both support our observations.

†Averages taken from the combined series of Holzapfel<sup>12</sup> and of Gusserow.<sup>25</sup>

tion and placenta previa, particularly with central previa, who have gone beyond 38 weeks of pregnancy. Such cases probably will be so rare as to cast considerable doubt upon any actual causal role that placenta previa might play in the persistence of breech presentation until or near to term.

TABLE II. THE POSSIBLE CAUSAL FACTORS OPERATING IN BREECH PRESENTATION, EXPRESSED IN PERCENTAGE OF OCCURRENCE, IN A RECENTLY PUBLISHED LARGE SERIES OF CASES,\* COMPARED WITH THE FINDINGS IN THE 76 PATIENTS PRESENTED IN THIS PAPER

	GROSS FETAL ANOM- ALIES	PLA- CENTA PREVIA	PELVIC TUMORS	UTERINE ANOM- ALIES	PLACENTA IMPLANTED OVER CORNUAL REGION OF UTERUS	TOTAL PERCENTAGE OF CASES IN WHICH THE CAUSE IS BELIEVED TO HAVE BEEN ESTABLISHED
Series of 677 cases <sup>4</sup>	1.6	1.2	0.6	0.6	Not men- tioned	4.0
Authors' series of 76 cases	0	0	0	1.4†	100	100

\*Tompkins' series<sup>4</sup> is used for comparison because it is large, extremely well worked out, and carefully analyzed.

†One case (Boston Lying-in Hospital X-ray No. 25400; see Fig. 4) had a heart-shaped bicornate uterus, with the placenta implanted entirely within the left half of the fundus and over the left cornu, and the fetal head occupied the right cornu. In this case both causal factors of breech presentation were acting simultaneously, and the case is thus included under both causal headings.

Another factor listed in Table II is fetal anomaly. Young<sup>7</sup> has shown that there is concurrence of gross fetal anomalies and breech presentation, and we have encountered cases in the past in which hydrocephalic fetal head was so distended as to be as large or larger than the breech of the fetus, and we have found breech presentation in such instances when the placenta was not implanted over either cornual region of the uterine wall. These rare cases establish marked hydrocephalus as an occasional cause of breech presentation, and other gross fetal anomalies, including large congenital tumors, may also play a causal role in breech presentation. We have been unable to find any instances in which pelvic tumors in the mother have been the principal cause of breech presentation, but we can readily understand how a large myoma in the cornual and fundal region of the uterine wall, on one side, could play such an etiological role, although as yet we have been unable to find such a case.

Anomalies of the uterus itself can definitely cause breech presentation, and the most common anomaly that does so is uterus bicornis. This is particularly true when one uterine horn is occupied by the placenta (Fig. 4). Such a case graphically portrays the mechanics of the situation; the cornual implantation of the placenta in one horn can make the fundal pole of the amniotic sac smaller than the lower uterine segment pole, and thus invite the permanent accommodation of the fetal head in the horn not filled by the placenta.

Since only about 59 per cent of breech deliveries are said to occur in multiparous women<sup>21</sup> and about 70 per cent of all infants are produced by multiparous women, it must follow that the factor of parity plays a certain definite role in determining whether or not any given fetus persists in presenting by the breech until or near to term. In Tompkins'<sup>4</sup> more recent studies of 677 breech deliveries it has been shown that 55 per cent of all of the infants weighing over 2,500 grams were born to formerly nulliparous (primiparous\*) women. Twenty-one per cent of the deliveries in his series took place in women having their second babies, 11 per cent in those having their third, and in those having their fourth, fifth, and sixth infants the figures were, respectively, 4, 2, and 3 per cent.

\*See last footnote under Table III.

TABLE III. PLACENTAL POSITION\* PLOTTED AGAINST PARITY IN 70 CASES OF BREECH PRESENTATION†

PAR-ITY‡	RIGHT CORNU AND FUNDUS				LEFT CORNU AND FUNDUS				TOTALS OF ALL CASES	TOTAL PRIMIP-ARAS AND MULTIP-ARAS
	DIRECT LAT-ERAL	PARTLY IN ANTE-RIOR FUNDUS	PARTLY IN POS-TERIOR FUNDUS	TOTALS	DIRECT LAT-ERAL	PARTLY IN ANTE-RIOR FUNDUS	PARTLY IN POS-TERIOR FUNDUS	TOTALS		
1	1	4	7	12	5	6	7	18	30	30 (43 per cent)
2	2	0	1	2	5	10	4	19	21	
3	1	0	1	2	3	2	1	6	8	
4	2	0	1	3	1	1	2	4	7	
5	0	0	1	1	0	0	0	0	1	40 (57 per cent)
6	0	0	0	0	1	0	1	2	2	
11	0	0	0	0	1	0	0	1	1	
Totals	6	4	11	20	16	19	15	50	70	70
	Ratio of Primiparas to Multiparas 12:8				Ratio of Primiparas to Multiparas 18:32					

\*See Fig. 1.

†Only 70 of our 76 cases are presented in this table because in six cases the clinical records were unavailable or incomplete.

‡Gravidas at or near term, the figure used being the parity they are shortly to attain.

In studying Table III, although it is plain that the cases are too few to be treated statistically, one notes the fact that 57 per cent of our patients are multiparas, which coincides fairly closely with the generally accepted figure of 59 per cent.<sup>21</sup> There is a decreasing incidence of breech presentations as parity increases, which is generally in harmony with the findings in Tompkins' series of 677 cases quoted above. Of more interest, for the purpose of this paper, is the fact that left cornual implantation of the placenta, in the cases shown in Table III, was two and one-half times as common as right cornual implantation.

Table III shows a marked reversal of ratio of primiparas to multiparas when the group with right cornual placenta is compared with the left-side group; in the right-cornu group this ratio is 12 to 8, while in the left-cornu group it is 18 to 32. In the right cornual group 12 out of the 20 patients were primiparas, while only two were secundiparas; in the left cornual group 18 out of 50 patients were primiparas, and 19 were secundiparas. Thus it appears that in secundiparas, and women of greater parity, when the placenta is implanted in the right cornual region, there is small chance of the fetal head remaining in, or rotating into, the empty left half of the fundus. In secundiparas with left cornual placentas, the fetal head appears to have a nine times greater chance of remaining in, or rotating into, the empty right half of the fundus, and this must be due to the right torsion of the upper portion of the uterus on its longitudinal axis. It is believed that this torsion of the uterus may increase slightly in degree with each successive pregnancy, the least amount tending to occur in primiparas. This belief, however, is supported by only a few observations made on the uteri of women upon whom we have performed repeated cesarean sections. In these cases we have noted slight progression to the right of the midline of each previous longitudinal scar in the uterus.

In this torsion process, the right half of the fundus and the right cornual portion of the uterus apparently tend to warp posteriorly around the lower vertebral column, resting against the mesentery of the cecum and the under-



lying right kidney. Such torsion, as pregnancy advances and the twisting increases, might in some way cause a decrease in the relative capacity of that pole of the amniotic sac which occupies the right half of the fundus (the left half being filled by the placenta) and thus tend to hold the fetal head there more securely. Conversely, the same right uterine torsion would tend to rotate, in a transverse plane, the left half of the fundus anteriorly away from the lower

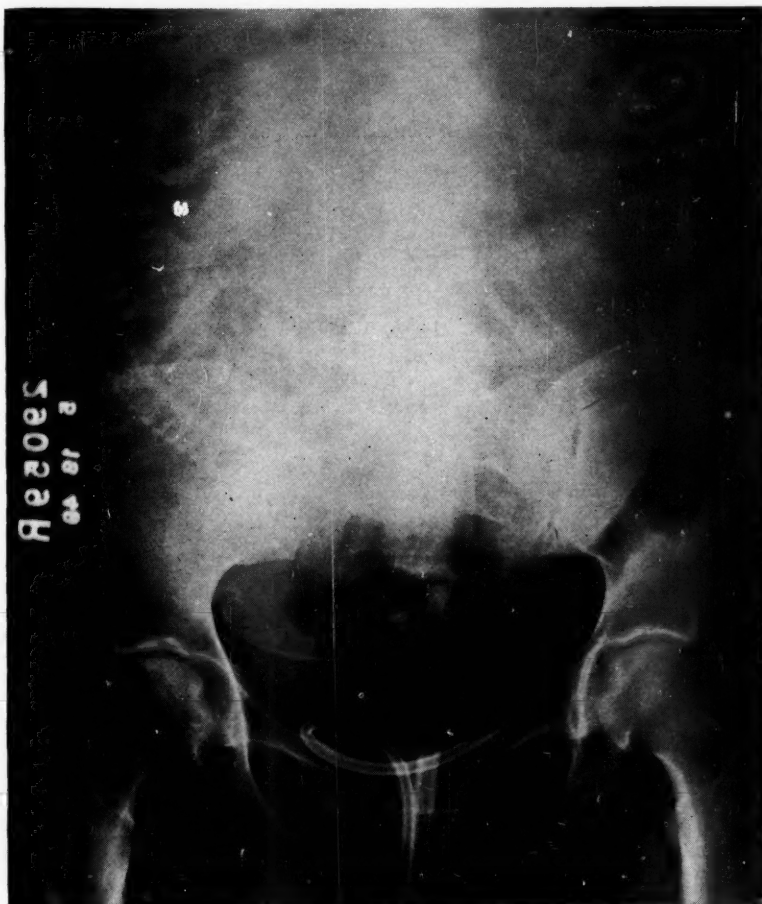


Fig. 3.—E. B., H.K.H. No. 101720, a 33-year-old gravida vii, para vi, had x-ray placentography because of slight vaginal bleeding. The placenta is seen to be implanted in the left cornual-fundal region, and the fetal head is presenting while the breech occupies the right half of the fundus. Although this patient was at term it was noted on rounds that her fetus might possibly undergo spontaneous version to breech presentation because of the left cornual-fundal implantation of the placenta. She was discharged and readmitted three days later in labor, and had a spontaneous breech delivery, the breech presenting left sacroanterior. The placenta, we know from our experience with x-ray placentography, lies in that portion of the area within the uterine wall outline which is not occupied by any fetal parts. This case exemplifies the positive effort of the fetus to accommodate itself best to the shape of the amniotic sac, i.e., the shape of the available fetal space.

pole of the left kidney and the spleen. When the placenta is implanted in the right cornual region, particularly (Table III) if part of the placenta extends over the upper anterior wall, the left half of the fundus might undergo a slight increase in capacity and thus tend to hold the fetal head less securely. This would promote spontaneous version of the fetus to cephalic presentation.

In any event, the facts shown in Table III demonstrate that right cornual implantation of the placenta permits the retention, in breech presentation, of

less than half as many fetuses as does left cornual placental implantation. To make a hypothetical reconstruction of what might have taken place in our series of 76 cases, let us take the figure of 2.95 per cent<sup>4</sup> for the incidence of breech presentation of babies weighing 2,500 grams or over at birth, which was the case in our series in so far as fetal weight was concerned. Using this figure for the incidence of breech presentation, our 76 cases of breech presentation would have come from a group of pregnant women calculated to have been about 2,580 in



Fig. 4.—M. B., B.L.I.H. X-Ray No. 25,400. The x-ray shows the unmistakable "saddle" contour of the uterine fundus characteristic of bicornate uterus. This contour is outlined in the above photograph by arrows. The placenta occupies the entire left uterine horn, while the fetal head lies in the right horn and the breech in the lower uterine segment. The fetus appears to have well accommodated itself to the shape of the amniotic sac within the heart-shaped uterus.

number. Let us next postulate, using Weisman's<sup>5</sup> figures, that, in the total group of women from whom our 76 cases were drawn, there were, at twenty-eight weeks of pregnancy, 206 fetuses still presenting by breech.\* During the next ten to twelve weeks about 130 of these fetuses were "released" from breech presentation, as a result, let us assume, of right torsion of the uterus and possibly the slight changes in uterine shape that go with its gradual increase in size as it approaches term. In the 206 cases in which the fetuses were presenting by breech at twenty-eight weeks of pregnancy, our knowledge to date would cause us to assume that in 103 of them the placenta was implanted over the right cornual portion of the uterus and in the same number over the left. According to the statistics stated under Fig. 1, 81 cases with right cornual

\*Table I shows a normal general occurrence of cornual placentas in 7 per cent of all cases, which figure is fairly well substantiated by Weisman's<sup>5</sup> figure of 8 per cent for the incidence of breech presentation at 28 to 30 weeks of pregnancy.

placentas would have "lost" their fetuses from breech presentation, or roughly 78 per cent, while 49 of the women with left cornual placentas "released" their fetuses, or 47 per cent.

The effect of increasing multiparity, and of the increasing relaxation of the uterus and anterior abdominal wall it confers, is a definite one in so far as persistency of breech presentation until term is concerned. Tompkins<sup>4</sup> figures for the decreasing incidence of breech presentation at or near term for each increased degree of parity show clearly that with increasing relaxation of the uterus it becomes less and less possible for a fetus to remain in breech presentation until term. We have no figures at hand which would show that the incidence of cornual implantation of the placenta decreases as parity increases, but we suspect that such is not the case. In previous soft-tissue x-ray studies of the pregnant uterus at term<sup>9</sup> we have found that with the increasing uterine and anterior abdominal wall relaxation of increasing parity the near-term pregnant uterus gradually tends to become more and more spherical and less and less a slightly flattened ovoid. As this basic change toward a generally spherical uterine shape increases with each succeeding pregnancy, a cornual implantation of the placenta has a decreasing restraining effect in preventing a fetus which is presenting by the breech from undergoing spontaneous version to cephalic presentation. This may be due to the fact that the flabby relaxation of the multigravid uterine wall might easily allow the fetal head to detour slightly and by-pass the placenta without much difficulty in its tendency to undergo spontaneous version to cephalic presentation.

Thus we believe that the human fetus tends to present cephalically whenever possible, and, to quote Vartan,<sup>2</sup> "that the breech presentation should be regarded as a persistence beyond the stage in pregnancy when to present by the breech is normal, and that the persistency is due to those factors which prevent spontaneous cephalic version from taking place."

### Summary

There are at least two factors which are causally operative in the persistence of breech presentation of the human fetus at or near term. The most important factor, cornual-fundal implantation of the placenta (called *tubenecken placentae* by Holzapfel<sup>22</sup>), was found, by soft-tissue x-ray placentography studies, to be present in all of the presented cases of breech presentation in the last two to three weeks of pregnancy. This cornual implantation site was confirmed in about 16 per cent of the cases by intrauterine palpation of the still in situ placenta just at the conclusion of the second stage of labor or at cesarean section. Since cornual implantation of the placenta was present in every case in our series of 76 women, it is the principal cause of breech presentation in single, term pregnancies.

The second factor is parity. Primiparity, in which the uterus is under full stretching tension for the first time, and in which the uterine shape tends to be definitely ovoid,<sup>9</sup> appears, on a relative basis, to favor breech presentation; multiparity, with its previously well-stretched uterus tending to be more spherical and less ovoid,<sup>9</sup> particularly after a woman has given birth to two previous infants, operates against the persistence of breech presentation until term.

A third, and as yet unproved, factor, namely right torsion of the uterus, is a condition generally accepted to be present in the third trimester in nearly

all pregnancies, and we have hypothesized that it plays a causal role in maintaining the persistence of breech presentation until term. This factor tends to prevent spontaneous version of the fetus to cephalic presentation when the placenta is implanted in the left cornu of the uterus. When the placenta lies in the right cornu, right torsion of the uterus is much less effective in preventing such spontaneous version of the fetus.

Multiparity, with its more spherical and relaxed uterus, tends to nullify markedly the roles played by both cornual implantation of the placenta and right torsion of the uterus in causing persistent breech presentation.

As a result of our findings in regard to the placental positions characteristically found in women with transverse or oblique fetal presentation<sup>9</sup> and in breech presentation a new obstetrical principle is proposed: *the position of the implanted placenta in the near-term, or term, human uterus, as it indents and alters the ovoid shape of the amniotic sac, determines the polarity of the sac independently of the fixed polarity of the containing uterus; functionally, the fetus accommodates itself to the shape of the sac, the fetal head seeking its smaller pole; and thus the placental implantation site has a determining effect upon the presentation of the fetus.*

### Conclusions

1. In a series of 76 cases of breech presentation at or near term we have demonstrated the in situ placenta to be implanted over one lateral fundal and tubal area of the uterine wall in all cases. We know (a) that such placental position has been found to be present in only 7 per cent (Table I) of all pregnancies, regardless of presentation of the fetus; (b) that about 8 per cent of all fetuses present by the breech at twenty-eight to thirty weeks of pregnancy<sup>5</sup>; (c) that by thirty-eight to forty weeks only 3 per cent of fetuses still present by the breech; and (d) that breech presentation must be regarded as a persistence beyond the stage in pregnancy when to present by the breech is normal, and that such persistency is due to those factors which prevent spontaneous cephalic version from taking place.<sup>2</sup> Thus we conclude that cornual-fundal implantation of the placenta is the principal cause of the persistence of breech presentation until term.

2. It has been found that the placenta was implanted in the left cornual region in 71 per cent of our cases, while in only 29 per cent was it implanted in the right cornu. We have advanced the hypothesis that right torsion of the body of the uterus on its longitudinal axis is responsible for this difference.

3. It has been shown that parity plays a definite role in determining whether or not a breech presentation persists until term; primiparity is found, relatively, to favor such persistence, while multiparity, particularly after a woman has given birth to two mature infants, militates against it. Multiparity, thus, tends to nullify the powers of both cornual implantation of the placenta and right torsion of the uterus in causing persistence of breech presentation until term.

4. With regard to the placental positions characteristically found in women with transverse or oblique fetal presentation<sup>9</sup> and in breech presentation, a new obstetrical principle is proposed: the position of the implanted placenta in the



near-term, or term, human uterus, as it indents and alters the ovoid shape of the amniotic sac, determines the polarity of the sac independently from the fixed polarity of the containing uterus; functionally, the fetus accommodates itself to the shape of the sac, the fetal head seeking its smaller pole; and thus the placental implantation site has a determining effect upon the presentation of the fetus.

The author wishes to acknowledge the encouragement and kindness of Dr. Duncan E. Reid, William Lambert Richardson, Professor of Obstetrics of Harvard Medical School; the help of Drs. E. Clark Gillespie, Charles L. Schneider, John B. Maunder, and Edwin F. Snider, all resident obstetricians at the Herman Kiefer Hospital; the kindness of Dr. Lewis E. Daniels, chief obstetrician of the Woman's Hospital, in placing the clinical material of that institution at the author's disposal; and the valuable criticism and helpful suggestions given by Dr. Walter H. Seegers, Professor of Physiology of Wayne University College of Medicine. To Mr. Charles Pickard, for his photographic reproductions of the x-rays, and to Miss Evelyn J. Erickson, for the illustrations, much appreciation is hereby expressed.

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1512 ST. ANTOINE STREET

## THE EXCESSIVELY LARGE FETUS AS AN OBSTETRIC PROBLEM\*

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WITHIN the past two decades, marked advance has been made in our concept and knowledge of the architecture of the female bony pelvis, as it affects the pregnant and parturient patient. As a result of the fundamental studies of Caldwell, Moloy, and D'Esopo, followed by those of Steele, Wing, Javert, McLane, and other workers in the field of x-ray pelvimetry, there have been added to our obstetric diagnostic armamentarium precise methods of measuring and evaluating the bony pelvis. It is now possible for obstetricians to predict with a great deal of accuracy what the outcome will be in a given case, for the capacity of that pelvis is readily estimated by x-ray pelvimetry. That this has been responsible for a marked improvement in our end results must be conceded.

Nevertheless, a hiatus still remains in our knowledge, for we have not as yet been able to evolve a method by which the exact size of the fetus can be ascertained prior to birth. Even before this problem is solved, it seemed important to answer the fundamental question, "Does the excessively large fetus really constitute an obstetric problem?" To that end, therefore, the present study was undertaken, in order to arrive at some fundamentally important conclusions from that standpoint.

If this study were to be of any value, it was felt that the differential in weight between the normal infant at birth and the excessive-sized infant should be so great that there would be no question whatever what role this excessive fetal weight plays in the production of the problem. In the past, a newborn infant was considered of excessive size if he weighed 4,000 grams or more (8 pounds, 13 ounces). However, a careful study of the literature was convincing enough to cause the choice of 4,500 grams (9 pounds, 15 ounces) as the lower limit of excessive weight, to furnish indisputably positive evidence for the part which it exerts during pregnancy and labor.

From 1932-1947, inclusive, 44,286 full-term infants were delivered at the New York Hospital. In this group, 756 weighed 4,500 grams or over, giving an incidence of 1.77 per cent of excessive-sized infants in all full-term deliveries.

### Distribution of Mothers

Of the entire series of 756 mothers, 607, or 80.30 per cent, were multigravidas, while 149, or 19.70 per cent, were primigravidas (Table I). Since this is not the usual ratio seen in the entire clinic, it would appear that we are

\*Read before the New York Obstetrical Society, May 10, 1949.

justified in stating that the multigravida is more prone to give birth to an excessively large infant than is her younger obstetric sister. This is in agreement with Wilson's study, in 1942, in which he found that multiparity plays an important part in the occurrence of unusually large children.

TABLE I. DISTRIBUTION OF MOTHERS DELIVERED OF EXCESSIVE-SIZED INFANTS

GRAVIDA	PER CENT
Primigravidas	19.70
Multigravidas	80.30

### Age Distribution of Mothers

From Table II, it will be seen that 459 mothers, or 60.71 per cent of all the patients, were between the ages of 26 to 35 years, inclusive, including primigravidas and multigravidas. This does not bear out the hitherto-prevalent impression that elderly patients are more prone to give birth to excessive-sized infants. In this series, less than two per cent of the mothers were over 40 years of age.

TABLE II. AGE DISTRIBUTION OF MOTHERS

PRIMIGRAVIDAS			MULTIGRAVIDAS		
AGE GROUP (YEARS)	NO. CASES	PER CENT	AGE GROUP (YEARS)	NO. CASES	PER CENT
17-20	21	2.78	18-20	10	1.32
21-25	56	7.41	21-25	80	10.58
26-30	46	6.08	26-30	199	26.32
31-35	19	2.51	31-35	195	25.79
36-40	6	0.80	36-40	111	14.68
Over 40	1	0.01	Over 40	12	1.58

### Sex Distribution of Excessive-Sized Infants

In the entire series, 521 infants, or 68.91 per cent, were boys, while 235, or 31.05 per cent, were girls (Table III). A similar observation has been made by Leon of Buenos Aires, whose ratio was almost identical with that of the present series. Other authors have recorded similar findings. Compared to this, the usually recorded ratios for all births are 50.40 per cent boys, and 49.60 per cent girls, or an almost equal distribution. Why more than two out of every three excessive-sized infants were boys must remain unexplained, at least until the geneticists are in a position to advance a plausible reason for such an occurrence.

TABLE III. SEX DISTRIBUTION OF EXCESSIVE-SIZED INFANTS

SEX	PER CENT
Males	68.91
Females	31.09

### Distribution of Weights of Excessively Large Infants

As will be seen from Table IV, 692 babies, or 90.53 per cent weighed from 4,500 to 5,000 grams, inclusive (9 pounds, 15 ounces, to 11 pounds), while 64, or 9.47 per cent, weighed over 5,000 grams (11 pounds), the largest one weighing 6,700 grams (14 pounds, 13 ounces).

TABLE IV. DISTRIBUTION OF WEIGHTS OF 64 INFANTS WEIGHING OVER 5,000 GRAMS

WEIGHT IN GRAMS	NO. CASES	WEIGHT IN GRAMS	NO. CASES
5,100	18	5,700	2
5,200	9	5,800	1
5,300	7	6,000	2
5,400	9	6,200	1
5,500	8	6,600	1
5,600	5	6,700	1

### Duration of Pregnancy

It is of course impossible, at least with the knowledge at present available, to estimate the exact duration of pregnancy. Nevertheless, if a patient gives an unequivocal menstrual history from the time the function was first established, and if she has had regularly recurring cycles at all times, considerable value must be attached to such a history. Accordingly, in this study, it was possible to collect 503 cases in which the menses were always regular at from 28- to 30-day intervals, with no aberration from the normal, since they first appeared.

Using this as a basis for estimating with reasonable accuracy the duration of pregnancy, it will be seen from Table V that 84.25 per cent of patients went beyond term, while in 48.90 per cent, or almost half the cases, the duration of pregnancy was 290 days or longer, with an average duration for the 503 cases, including primigravidas and multigravidas, of 289.46 days. Furthermore, from Table VI it will be seen that in about 32 per cent of the cases the pregnancy was prolonged to 300 days or more. In addition, in six multigravidas, the pregnancy went beyond 320 days, the longest of these being 325 days in two cases, while the longest duration in the primigravidas was 320 days in one case.

TABLE V. DURATION OF PREGNANCY

GRAVIDA	TOTAL NO. CASES	BEYOND TERM	BEYOND 290 DAYS
Primigravidas	107	87.85 %	56.07 %
Multigravidas	396	79.90 %	46.96 %

Among factors which might be responsible for the abnormal prolongation of pregnancy beyond the expected date of delivery, one explanation might be an abnormally prolonged activity of the corpus luteum, or the intervention of the anterior pituitary, which might occur spontaneously in subjects with an endocrine taint. Murphy, in 1944, recorded a case in which large amounts of corpus luteum had been administered in the first half of pregnancy, in order to control a threatened abortion. The pregnancy progressed for forty-four weeks, and the infant was unusually large at birth.

TABLE VI. PROLONGED DURATION OF PREGNANCY OF 300 DAYS OR MORE

GRAVIDA	NO. CASES	PER CENT
Primigravidas	19	17.75
Multigravidas	56	14.14



Greenhill also states that he has observed that women who have received large amounts of progesterone during pregnancy have a tendency to go beyond the calculated date of delivery. Hence the question arises whether a determination of the pregnandiol content of the urine would be of value in determining a suspected prolongation of pregnancy. Likewise, since stilbestrol is now being employed in very large doses in cases of threatened abortion, up to the thirty-fifth week, and since it is also administered to patients who give a history of repeated abortions, is it possible that the pregnancy might be prolonged unduly by such therapeutic measures?

It would, therefore, be of interest to study a series of patients who have received enormous doses of stilbestrol during pregnancy, and to see whether they actually tend to go beyond the expected date of delivery, since the administration of stilbestrol is predicated on the theory that it causes an increased secretion of progesterone in human pregnancy (probably by the placental syncytium) through causing an increased utilization of chorionic gonadotropin. As O. W. Smith has pointed out, an important part of the understanding of this concept is the realization that stilbestrol is given, not because it is estrogenic, but because it stimulates the secretion of estrogen and progesterone.

Admitting that memory on the part of the patient may be fallacious, either by omission or commission, certain medicolegal implications present themselves with the problem of prolonged pregnancy. The legitimacy of the child might be questioned if the pregnancy were unduly prolonged, where the husband had been absent for a considerable length of time. However, if the infant were of excessive size, considerable significance would have to be attached to this, before the child could with justice be considered illegitimate.

The careful and conscientious obstetrician must be steadfast in resisting attempts to stampede him into inducing labor in the case of a prolonged pregnancy. Nevertheless, when the fetus appears to be of excessive size, and when the pregnancy has gone three weeks beyond the expected date of delivery, and careful vaginal examination at this time shows the cervix to be effaced and partially dilated, it would seem to be justifiable to induce labor, provided the pelvis is found to be ample in size, and no other contraindications are present. Certainly a history of a previous difficult delivery, with an excessively large infant, either deadborn, or seriously injured, should lead to very serious consideration of delivery by Cesarean section, in the presence of a second excessively large fetus. The conclusions herein arrived at are in agreement with those of Wilson, who also advises the more frequent employment of cesarean section, especially if the pregnancy appears to be prolonged and the baby very large.

### Maternal Weight Changes

Various authorities have placed the average maternal weight gain in pregnancy at about 11 kilograms or 24.2 pounds. From Table VII it will be seen that about 50 per cent of the mothers in this series showed such a gain, while about 50 per cent showed a gain of 12 kilograms (26.4 pounds) or more. Furthermore, almost 27 per cent showed an excessive gain of 15 kilograms (33 pounds) or more. Hence, since at least one out of every four patients who were delivered of excessively large infants showed an excessive gain in weight during pregnancy, it would appear that an excessive maternal weight gain would be of considerable significance in forecasting the birth of an excessively large fetus, especially if it is associated with a prolonged pregnancy. From the standpoint of the size of the fetus, a flat plate of the mother's abdomen might be of some value in arousing the suspicion of the presence of an excessively large infant, if the x-ray showed fetal hyperflexion, necessitated by lack of space in the uterus.

TABLE VII. WEIGHT CHANGES IN MOTHERS DELIVERED OF EXCESSIVE-SIZED INFANTS

WEIGHT CHANGES	NO. CASES	PER CENT
Loss of weight	4	0.56
No change in weight	1	-----
Average normal weight gain of 11 kilograms (24.2 pounds)	349	49.08
Gain of 12 kilograms (26.4 pounds)	357	50.02
Excessive Gain of 15 kilograms or more (33 pounds)	191	26.86

### Rh Status of Mothers

The number of mothers in whom the Rh status was known is too small to furnish any definite conclusions as to the relation of the factor to the excessive-sized fetus (Table VIII). Many of the mothers in this series were delivered prior to the time when it became routine to ascertain the Rh status. In the 184 mothers whose Rh factor was known, approximately 90 per cent were positive, and about 10 per cent were negative. Of the known Rh-positive mothers, 24 each gave birth to two babies of excessive weight, while, of the Rh-negative mothers, 4 each gave birth to two babies of excessive weight, and 1 gave birth to three excessively large infants.

TABLE VIII. RH STATUS OF 184 MOTHERS IN WHOM THE RH FACTOR WAS KNOWN

RH STATUS	NO. CASES	PER CENT
Positive	165	89.68
Negative	19	10.32

### Duration of Labor

Up to the present time it has been customary to expect a longer than normal labor in the presence of an excessively large fetus. Indeed, in the very last edition of his textbook, Greenhill states that labor is slow in such cases. The findings in this series definitely nullify such a concept. From Table IX, it will be seen that in 718 cases in which the duration of labor was recorded accurately, 534 patients, or 74.37 per cent, were delivered in 18 hours or less, while 609 patients, or 84.81 per cent, were delivered within 24 hours after the onset of labor. Thus the conclusion can be drawn that an excessively large fetus per se does not prolong unduly the duration of labor. This is in agreement with the findings of Biro in 1944.

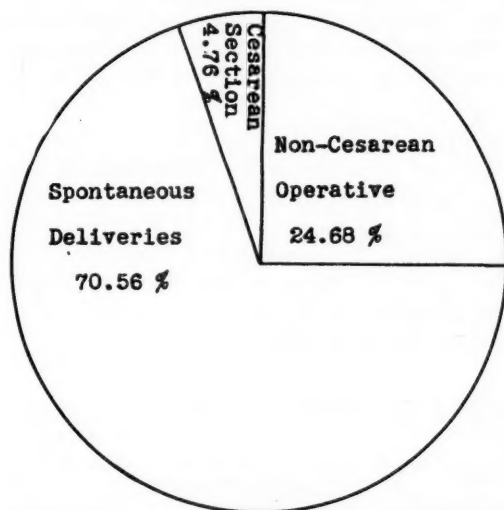
TABLE IX. DURATION OF LABOR

SIX-HOUR INTERVALS	NO. CASES
Less than 6 hours	191
6-12 hours	200
12-18	143
18-24	75
24-30	25
30-36	36
36-42	12
42-48	11
48-54	5
54-60	12
60-66	3
66-72	1
72-78	2
78-84	1
84-90	1

### Method of Delivery of Excessive-Sized Infants

From Fig. 1, it will be seen that spontaneous delivery occurred in 70.56 per cent of the cases, while operative delivery, cesarean and noncesarean, was resorted to in 29.44 per cent. A further breakdown of the operative procedures shows that cesarean section was employed in 4.76 per cent of the cases, compared with a clinic incidence of 3.30 per cent.

It is at this point that reference must be made to the serious bony and neurological injuries which the excessively large infants incurred, and to their infantile mortality. The total number of serious infantile injuries observed was 25 in 716 living babies, or in 3.49 per cent of the total number. If with this very high figure there is associated the high infantile mortality of 5.82 per cent, compared with that of 3.10 per cent for the entire clinic, it is at once apparent that something must be done to bring both of the above findings more in line with what is now being attempted by all of us, namely, a reduction in the infantile morbidity and mortality.



DELIVERIES OF 756 EXCESSIVE SIZE INFANTS

Fig. 1.

It is important to remember that the entire clinic infantile mortality of 3.10 per cent includes premature infants, in whom all will acknowledge there is a much higher infantile mortality than is present in full-term infants. If, therefore, the entire clinic figure were to be corrected, it is certain that the infantile mortality of the excessive-sized babies would be at least twice as high as that of the entire clinic. Thus, in looking about for a factor with which this abnormally high infantile morbidity and mortality can be directly associated, we are forced to the inescapable conclusion that the difficult delivery by the vaginal route plays a very important role in their production.

Hence it would seem reasonable to employ cesarean section more frequently in order to attain our objective of a lower infantile morbidity and mortality. Another objective which such a procedure would accomplish would be to decrease the serious injuries to the maternal soft parts, so frequently seen in the difficult deliveries of excessive-sized infants per vaginam, with their associated high incidence of postpartum hemorrhage and shock incident to severe lacerations of the vaginal tract and of the lower uterine segment.

### Relation Between Postpartum Hemorrhage and the Delivery of Excessive-Sized Infants

In the Woman's Clinic of the New York Hospital, postpartum hemorrhage is considered to have occurred in all cases, excluding cesarean section, in which the blood loss has been 600 c.c. or more. Using this figure as a guide, the incidence of postpartum hemorrhage in the entire clinic during the years covering this study (1932-1947), was 3.00 per cent. In this series, excluding those patients who were delivered by cesarean section, 75 patients out of 720 delivered by the vaginal route had postpartum hemorrhages. This is an incidence of 10.4 per cent, or about three and one-half times the incidence in the entire clinic (Table X).

Thus we are justified in concluding that there is an indisputable, and, indeed, a very important relationship between the birth of an excessive-sized infant and postpartum hemorrhage. Certainly, the marked discrepancy herein reported cannot be looked upon as a mere coincidental finding. That this very high incidence is due not alone to atony of the uterus is attested to by a study of the individual records of the cases of postpartum hemorrhage. In many instances, the difficulty encountered during a vaginal delivery was productive of serious lacerations of various parts of the genital tract, with resultant excessive blood loss.

This, therefore, reinforces the observation previously made that a higher incidence of cesarean section appears to be warranted, if the serious menace of postpartum hemorrhage and shock is to be avoided. The practical lesson to be learned from this study would seem to be the routine typing of every patient in whom an excessively large fetus is suspected, with sufficient compatible blood, readily available in the delivery room at the time of delivery. With such a precaution, it would be possible to avert, or to combat, if necessary, the ever-present menace of postpartum hemorrhage.

TABLE X. INCIDENCE OF POSTPARTUM HEMORRHAGE EXCLUSIVE OF CASES OF CESAREAN SECTION

GROUP	PER CENT
Entire clinic	3.0
Excessive-sized infants	10.4

### Serious Injuries to Excessively Large Infants

That shoulder dystocia is encountered in a very high number of cases of excessive-sized infants delivered by the vaginal route is at once apparent from a study of the cases in this series. Difficulty in delivering the shoulders or arms occurred in 76 out of 720 vaginal deliveries, or in 10.55 per cent of the cases. Furthermore, the total number of serious infantile injuries which were encountered in the series was 25 out of 716 living infants, giving an incidence of 3.49 per cent of the excessive-sized infants delivered by the vaginal route.

From Table XI, it will be seen that these injuries are divided into bony injuries, and serious neurological lesions. The former involved fractures of the humerus in 4 cases, and fractures of the clavicle in 8 cases. Of the serious neurological lesions, Erb's paralysis occurred in 7 cases, 1 of which showed a bilateral lesion, while a flaccid paralysis of the arm was present in 2 cases. In addition, complete paralysis of one arm and hand, with no x-ray indication of fracture occurred in 1 case, and brachial plexus paralysis was present in 3 cases.

This very high incidence of serious infantile injuries associated with delivery by the vaginal route, calls for serious consideration of more frequent



resort to delivery by the abdominal route. In addition, more attention should be directed to the training of residents in proficiency in dealing with the problem of shoulder dystocia, where delivery per vaginam has been decided upon. Furthermore, it would seem advisable to have a routine x-ray examination of the shoulder girdle in every case where difficulty was encountered with the deliveries of the shoulders or arms, in order to detect silent fractures.

TABLE XI. SERIOUS INJURIES TO EXCESSIVE-SIZED INFANTS

<i>Bony Injuries</i>	
Fracture of humerus	4 cases
Fracture of clavicle	8 cases
<i>Serious Neurological Lesions</i>	
Erb's paralysis	7 cases
(One case of bilateral Erb's)	
Flaccid paralysis of the arm	2 cases
Complete paralysis of one arm and hand (with no x-ray indication of fracture)	1 case
Brachial plexus paralysis	3 cases

It must likewise be reiterated, and with emphasis, that serious lacerations of the genital tract due to difficulty in delivery of the arms or shoulders play a very important part in causing the high incidence of post-partum hemorrhage. It is significant to note that cleidotomy was resorted to in only two cases, and these in stillborn infants. Thus the question arises whether this procedure, which seems to have been relegated almost to oblivion, might not with considerable profit be employed more frequently in order to decrease to the minimum serious injuries of the maternal soft parts, and also to facilitate the delivery of the arms and shoulders. Certainly, an intentional fracture of the arm or clavicle would be more advisable than an almost brutal pull from below or badly directed pressure from above, with irreparable damage to the baby and serious blood loss to the mother.

### Complications in Pregnancy in Mothers Delivered of Excessive-Sized Infants

TABLE XII. COMPLICATIONS OF PREGNANCY IN MOTHERS DELIVERED OF EXCESSIVE-SIZED INFANTS

<i>Toxemia</i>		83 Cases
Hypertensive disease	15	
Chronic nephritis	4	
Low reserve kidney (old classification)	15	
Mild pre-eclampsia	19	
Severe pre-eclampsia	12	
Eclampsia	1	
Hyperemesis gravidarum	1	
Acute yellow atrophy	1	
Unclassified toxemia	15	

TABLE XIII. COMPLICATIONS OF PREGNANCY IN MOTHERS DELIVERED OF EXCESSIVE-SIZED INFANTS

<i>Constitutional Diseases</i>		40 Cases
Heart disease	13	
Thyrotoxicosis	1	
Graves's disease	1	
Idiopathic epilepsy	2	
Pulmonary tuberculosis	2	
Diabetes*	21	
<i>Other Complications</i>		8 Cases
Polyhydramnios	4	
Placenta previa	4	

Tables XII and XIII show in detail the maternal complications, and it is significant to note that toxemia was present in 10.97 per cent, compared to a clinic incidence of 8.60 per cent, which, however, includes late miscarriages, premature deliveries, etc. Of even greater interest is the fact that, whereas the clinic incidence of maternal diabetes was only 0.30 per cent, the incidence of diabetes in this series was 2.77 per cent, or nine times as high as in the entire clinic clientele.

### Maternal and Infantile Mortality

From Table XIV it will be seen that the maternal mortality in this series was 2.64 per thousand, compared to 1.4 per thousand for the entire clinic, or almost twice as high in the cases with excessively large infants. In both of the maternal deaths, careful review of the case records shows that postpartum hemorrhage, due to atony of the uterus, following cesarean section, was responsible for the deaths. However, it also shows that they would in all probability have been averted if hysterectomy had been performed before irreversible shock had made it imprudent. Both of the deaths occurred at from two and one-half to four and one-half hours after delivery, and post-mortem examination failed to disclose any other cause for the deaths except uterine atony for which the patients had been packed at the time of operation.

TABLE XIV. MATERNAL AND INFANTILE MORTALITY

GROUP	MATERNAL MORTALITY	INFANTILE MORTALITY
Entire clinic	1.4 per thousand	3.1% includes premature infants
Excessive-sized infants	2.64 per thousand	5.82%

As previously stated, the infantile mortality for the series was 5.82 per cent uncorrected, or almost twice as high as that of the entire clinic, which, however, includes premature infants. Of the 44 infants that died, twenty-four were deadborn, sixteen were stillborn, and four died in the neonatal period.

Wilson, in 1942, had an infantile mortality rate of 4.8 per cent, but in so far as 80 per cent of his series were babies whose weight began at 4,000 grams, it is reasonable to state that the greater the weight of the fetus, the higher the infantile mortality, since the present series consists of excessive-sized infants beginning with a minimum weight of 4,500 grams. This is clearly demonstrated by the fact that whereas only about 10 per cent of the 756 infants in the entire series weighed over 5,000 grams, 31.8 per cent of the infant deaths occurred in this group. Thus we are in complete agreement with Wilson, who states that the fetal death rate increases rapidly for every 500 grams above 4,500, becoming unduly high in those weighing 5,000 grams or over. It is also significant to note that 41.33 per cent of the infant deaths occurred in pregnancies which were prolonged beyond 290 days, an important aspect to keep in mind when one is considering the advisability of interrupting the pregnancy.

### Summary and Conclusions

1. From this study, there is incontrovertible evidence that the excessively large fetus constitutes a definite obstetric problem, sufficient at times to tax the ingenuity of even the most experienced obstetrician.

2. Adopting 4,500 grams as the lower limit of excessive-sized infants, there were 756 cases in 44,286 deliveries at the New York Hospital, between 1932 and 1947, inclusive. This is an incidence of 1.77 per cent of all full-term deliveries.

3. Primigravidas accounted for about 20 per cent, and multigravidas for about 80 per cent of the series.

4. About 60 per cent of all the excessively large infants occurred in mothers between the ages of 26 and 35 years, inclusive.

5. There were more than twice as many male infants as there were females.

6. Ninety per cent of the infants weighed between 4,500 and 5,000 grams, inclusive, while about 10 per cent were over 5,000 grams, the largest one weighing 6,700 grams.

7. Including both primigravidas and multigravidas, out of a total of 503 patients in whom the duration of pregnancy could be determined with reasonable accuracy, about 85 per cent went beyond term, while in about 50 per cent the duration of pregnancy was 290 days or longer, and in about 32 per cent the pregnancy was prolonged to 300 days or more.

8. An excessive gain in the maternal weight during pregnancy appears to be of considerable significance in forecasting the birth of an excessively large infant, since at least one out of every four mothers showed an excessive gain of 15 kilograms (33 pounds) or more.

9. An excessively large fetus per se does not prolong unduly the duration of labor.

10. Postpartum hemorrhage was three and one-half times as frequent in this series as compared to the incidence in the entire clinic.

11. Serious infantile injuries, including bone injuries and neurological lesions, occurred in 3.5 per cent of excessively large living infants.

12. The maternal and infantile mortality was almost twice that of the entire clinic.

13. It would appear from this study that an increase in the incidence of cesarean section would be justified, since a marked reduction could thereby be obtained in the incidence of postpartum hemorrhage, serious infantile birth injuries, and infantile mortality.

14. Diabetes was encountered nine times as frequently in the mothers of excessively large infants as in the general clinic clientele.

15. Since great difficulty was encountered in delivering the arms or shoulders in 10.55 per cent of the cases, routine x-ray examination of the baby's shoulder girdle in such cases would be of value in detecting silent fractures in this region.

16. Routine cross-typing of every patient in whom a large baby is suspected, with sufficient compatible blood readily available in the delivery room at the time of delivery, would constitute a real prophylactic measure, in combating the high incidence of postpartum hemorrhage.

17. No inflexible rules can be laid down for the routine conduct of labor in the patient with an excessively large fetus. Individualization of each case, using the experience, judgment, and ability of the attending obstetrician, with the adoption of the recommendations made from this study, is presented as an ideal approach to the solution of the problem.

## A STUDY OF THE CHANGES IN THE CYTOLOGY OF THE URINARY SEDIMENT DURING THE MENSTRUAL CYCLE AND PREGNANCY\*

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IT HAS been known for several years<sup>1</sup> that the epithelium of the human vagina undergoes certain changes during pregnancy which are most clearly observed in the exfoliated cells of the vaginal smear. The characteristic forms of pregnancy consist of elongated, concave, boat-shaped cells with totally or partially vacuolated cytoplasm and flattened elongated nuclei, the so-called navicular cells. The value of these changes as a criterion for the diagnosis of pregnancy is, however, lessened by the presence of mucus, leucocytes, bacteria, abundant superficial cells, and, at times, infection. These factors tend to obscure and sometimes alter the cellular changes that might be considered characteristic of pregnancy.

A great stimulus to the study of exfoliated cells of the various body surfaces and cavities has arisen from the discovery that cancer cells may be identified in these exfoliations. As a result of this interest, Papanicolaou,<sup>2</sup> in examining the urine of men with prostatic carcinoma receiving estrogenic therapy, noted changes in the cytology of the urinary tract similar to those that occur in the vaginal cytology upon estrogenic stimulation. Essentially, these changes consist of an increase in superficial cells, acidophilia, pyknosis, cytoplasmic granules, and vacuolation due to increased glycogen content. In 1948, Papanicolaou<sup>3</sup> reported that the marked hormonal alterations of pregnancy also affected the cytology of the urinary sediment and suggested that, with the interfering factors in the vaginal smear absent, the changes in cytology might offer a reliable means of diagnosing pregnancy.

Our study was undertaken to determine the characteristics of the exfoliated cells of the urinary tract during pregnancy and to ascertain their diagnostic value. We have also attempted to correlate the cytologic changes with the variations in hormonal levels that occur in pregnancy. Also, in studying urinary smears from nonpregnant women to establish a normal, we found cyclical changes that can be correlated with the menstrual cycle and this paper gives a preliminary report on these cellular changes.

### Methods

Urine was obtained by catheterization from women patients visiting the Obstetrical and Gynecological Clinics of the Colorado General Hospital Out-Patient Department. Catheterized specimens were used to minimize the con-

\*Abridgment of thesis submitted by Dr. McCallin to the Faculty of the Graduate School of the University of Colorado in partial fulfillment of the requirements for the degree of Master of Science in Physiology.



tamination by vulval and vaginal cells which often occurs when urine is voided by women.

An equal amount of 95 per cent alcohol was added immediately after a specimen was obtained to delay disintegration of the exfoliated cells which is ordinarily rapid. With a delay of no longer than two or three hours, this alcohol-urine mixture was centrifuged at a moderate speed for thirty minutes. The supernatant liquid was decanted and the sediment was spread thinly on slides cleaned in 95 per cent alcohol and coated with a thin layer of Mayer's albumin. The smears were immediately placed in a fixative of equal parts ether and 95 per cent alcohol. Following fixation for at least fifteen minutes, the smears were stained by a modification of Papanicolaou's method.<sup>4</sup> Harris' hematoxylin, Orange G6, and EA 50 were the stains used.

### Cytology of Urinary Smears

#### 1. *During the Menstrual Cycle.*—

Because descriptions in the literature of the exfoliated cells of the urinary tract refer only to the unstained smear, we began our study with an examination of smears from normal nonpregnant women.

Though the vagina is covered by stratified squamous epithelium and the urinary tract by transitional epithelium, it was found that the exfoliated cells of the urinary tract could be fitted nicely into Papanicolaou and Traut's<sup>5</sup> classification of the cell types in the vaginal smear. They divided the exfoliated cells of the vaginal epithelium into three groups, the parabasal or outerbasal type derived from the upper layers of the basalis zone of the vaginal epithelium as seen in section, the intermediate cell type from the upper basalis and intra-epithelial zones, and the superficial type from the more superficial and cornified zones. Occasionally cells from the deepest basilar layer were noted, the inner basal type. The basal and intermediate cell types in the urinary smears were found to resemble closely the description of similar types in the vaginal smear. However, the superficial types differed considerably. The cornification and marked acidophilia prominent in the vaginal smear were absent. Groups of outer basal cells are seen in Fig. 5. Fig. 2 shows examples of intermediate cells, and Figs. 1 and 2 demonstrate the appearance of the superficial type.

Schmidlapp and Marshall<sup>6</sup> consider cells in the urinary sediment to be almost completely of bladder origin because in their study of urinary smears bladder neoplasms were diagnosed correctly in a high percentage of cases, but renal tumors were frequently missed. Normal renal cells are less likely to be found than malignant renal cells because neoplastic cells desquamate more readily and such was our experience. Leucocytes are absent unless infection is present. Histiocytes are occasionally found. In general, the urinary smear is much less cellular than the vaginal smear; the cells are more basophilic and anucleated cornified superficial types are not seen.

With a classification of the cell types found in urinary sediment established, a description of the cells seen in the nonpregnant woman during active sexual life is more clear. Specimens were obtained from 31 women at various times during their menstrual cycles. As expected from the literature on the vaginal smear,<sup>7, 8, 9</sup> considerable variation was found and it was possible to relate these changes to the different phases of the menstrual cycle.

In the early follicular stage, about the sixth or seventh day of the menstrual period, few cells were found in the urinary smear. They consisted mainly of superficial cells with a few intermediate cells, both types having transparent basophilic cytoplasm with granular to compact central nuclei. Cytoplasmic granules and vacuoles were rare. Cells occurred singly or in groups of two to

three. As the menstrual period advanced the superficial cells increased in number. Basophilia was still generalized, but an occasional cell was acidophilic. Nuclei became more compact and even pyknotic. Granules and vacuoles increased steadily in number (Fig. 1).

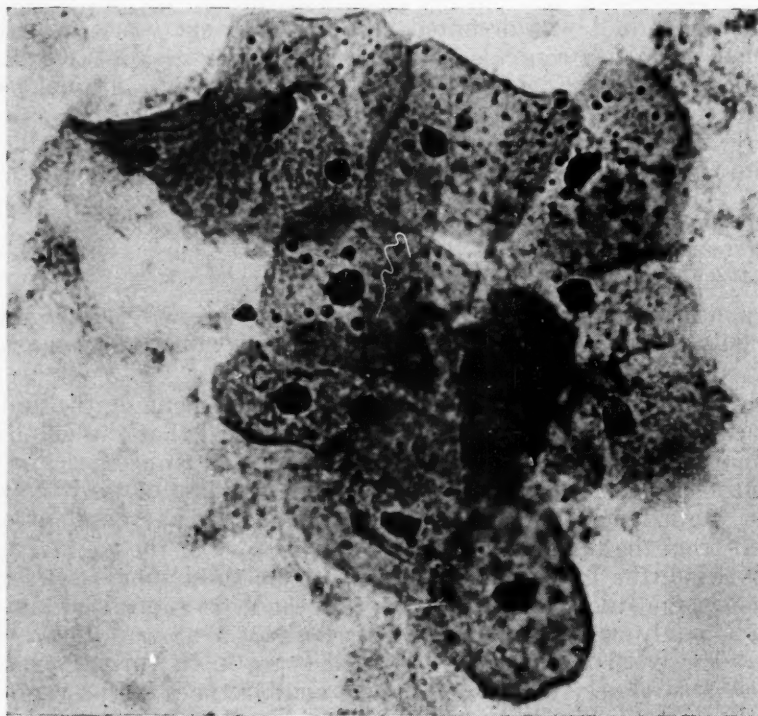


Fig. 1.—Superficial cells obtained on the twelfth day of the menstrual cycle (follicular phase). ( $\times 600$ .)

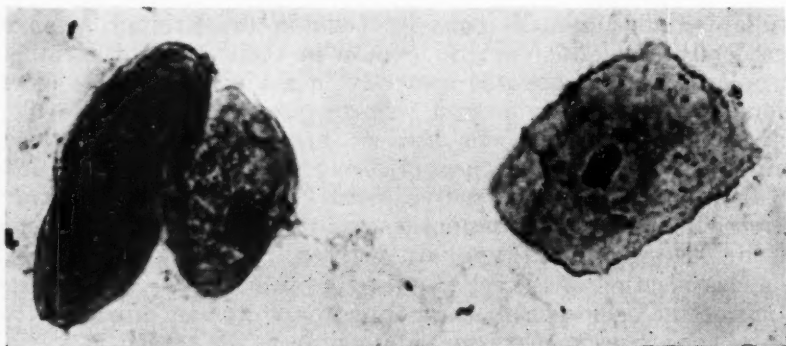


Fig. 2.—Group of intermediate cells and single superficial cell obtained on the eighteenth day of the menstrual cycle (postovulatory phase). ( $\times 600$ .)

No specific changes appeared to mark the day of ovulation but there was a gradual modification of the cytology in the postovulatory phase. Cells continued to show pyknotic and compact nuclei with vacuolated cytoplasm and occasional granules, but others appeared with enlarged, less compact nuclei, and there was a tendency to wrinkling. As the period progressed, wrinkling

of cells became more prominent and clusters of five to ten cells were more frequent. Intermediate cells became more numerous (Fig. 2). Basophilia remained the predominant staining reaction.

As the premenstrual phase (four to five days before menstruation) approached, cellularity was considerably increased with an apparent desquamation of all cell types. Superficial cells were still seen but they were outnumbered by intermediate types, many with translucent cytoplasm, granular nuclei, and heavy contours (Fig. 3) that were sometimes confused with the navicular cells of pregnancy (Fig. 4). Wrinkling was evident, although not so prominent as earlier, but clustering of cells was increased. Cells with enlarged vesicular nuclei, sometimes double, and deeply basophilic cytoplasm were observed (Fig. 5). The cytologic pattern was rapidly transformed after the menstrual flow commenced into one resembling the early follicular smear with only a few scattered cells.

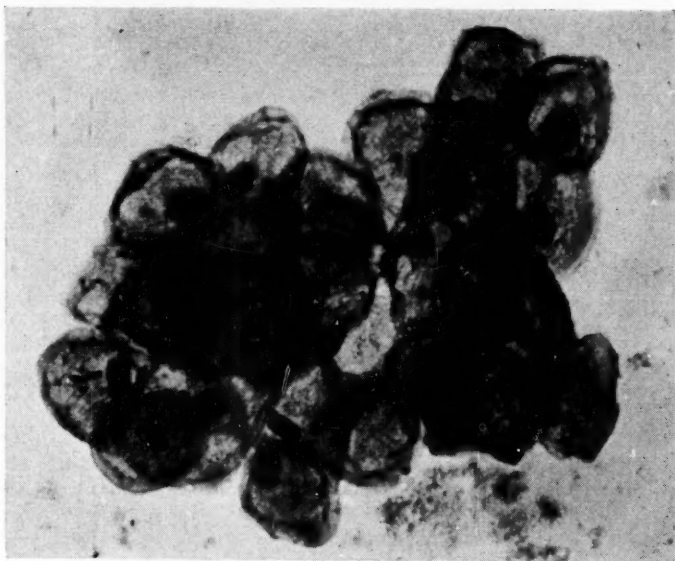


Fig. 3.—Intermediate cells obtained on the seventeenth day of a twenty-one-day menstrual cycle (premenstrual phase). ( $\times 600$ .)

The changes in the urinary smear during the menstrual cycle seem to differ from those in the vaginal smear in that an apparent desquamation occurs in the premenstrual phase and is completed early in the menstrual phase while in the vaginal smear, the desquamation occurs mainly in the latter phase.

## 2. During Pregnancy.—

In the study of the cytology of urinary sediment during pregnancy, catheterized specimens were obtained from seventy-seven women at all stages of pregnancy, from one week after the first missed menstrual period to immediately before delivery. There was considerable variation at different stages of pregnancy as well as individual variation, but typically the pregnancy smear presented a heavy cellularity with about equal numbers of superficial and intermediate cells. The superficial cells showed variable staining, but ordinarily were more acidophilic than in the nonpregnant state. Basophilia was, however, the predominant reaction. Most helpful in the diagnosis of pregnancy was the

navicular cell, a modification of the intermediate cell type. These cells were elongated, spindle-shaped, concave, and boat-shaped in form, had heavy doubly refractive boundaries, and were generally smaller than the intermediate cells of the nonpregnant state. Nuclei were larger, compact or pyknotic, elongated and often flattened against the periphery. The cytoplasm appeared vacuolated or quite clear due to the presence of one large vacuole filling the entire cell which pushed the nucleus to the periphery. Staining was ordinarily basophilic, but acidophilic cells were seen occasionally. Wrinkling was uncommon, but densely packed clusters of navicular cells were very typical (Fig. 6). Fig. 4 shows less typical navicular cells from the first half of pregnancy.



Fig. 4.—Navicular cells from a woman 5 months pregnant. ( $\times 600$ .)

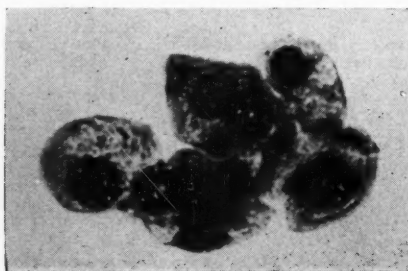


Fig. 5.—Outer basal cells obtained on the twenty-fourth day of the menstrual cycle (premenstrual phase). ( $\times 600$ .)

Unfortunately, the premenstrual smear (Fig. 3) often contained cells closely resembling the navicular cells of early pregnancy (Fig. 4), and thus the diagnosis of pregnancy from the study of the urinary sediment was unreliable. In specimens obtained at or before two months of pregnancy, of which the earliest was three weeks, the cytology was not specific for pregnancy, but more generally resembled the premenstrual smear. There was individual variation. As pregnancy advanced into the third and fourth months, typical navicular cells were



more commonly seen, though not until about six to seven months were dense clusters of these cells seen. Also, the navicular cells appeared smaller as pregnancy advanced. The superficial cells did not show marked nuclear pyknosis, vacuolation, and cytoplasmic granules with increased eosinophilia until six months of pregnancy. There was then an increase of these characteristics up to the ninth month. As criteria for the diagnosis of pregnancy, navicular cells appeared earlier than did the changes in the superficial cells. The number of navicular forms as compared with superficial types ordinarily increased as pregnancy advanced, but an occasional smear in the last trimester showed only infrequent navicular forms.

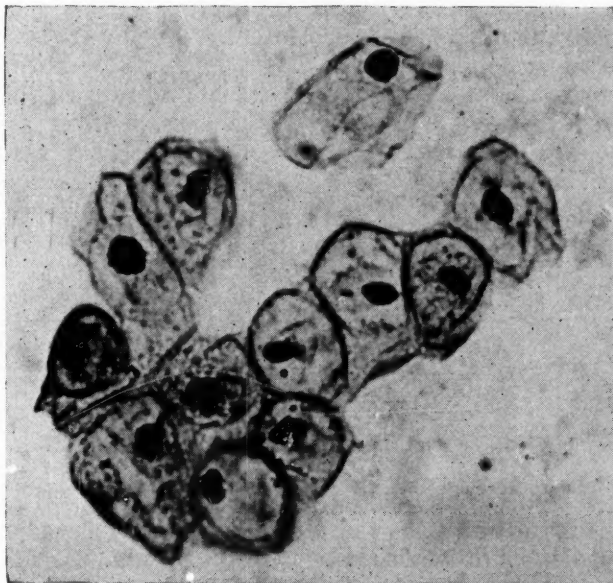


Fig. 6.—Navicular cells from a woman 7½ months pregnant. (×600.)

Considering the possibility that hormonal changes which may occur prior to the onset of labor would be reflected in the cytology of the urinary sediment, we obtained weekly urine specimens from two to four weeks before term up to delivery in fourteen patients. Up to a week before delivery, these smears showed merely the characteristics of the last trimester of pregnancy, but specimens obtained within the last seven to eight days showed several characteristic changes. There was a definite increase in cellularity with the presence of sheets of navicular and superficial cells. Most striking, however, was the appearance of variable-sized and irregularly shaped cells with large vesicular nuclei, often two or three to a cell (Fig. 7). The larger cells exceeded the superficial cells in size. The cytoplasm stained a deep pink to orange or sometimes blue. Usually it was homogeneous, though occasional vacuoles were observed. In the smaller cells the nuclei exceeded half the cell area. These cells were found in moderate numbers the last week of pregnancy, increased greatly after the onset of labor, and persisted after delivery. They conformed to the description by Papanicolaou<sup>7</sup> of what he called postpartum cells. Such cells were found in the vaginal smears taken after delivery and up to ten days post partum.<sup>7</sup>

In urinary smears obtained twenty-four to forty-eight hours prior to the onset of premature labor in two patients, these so-called postpartum cells were also observed.

Apparently an extensive desquamation of the epithelium of the urinary tract precedes and accompanies the onset of labor. Such a phenomenon has evidently not been observed in the human vaginal epithelium,<sup>10</sup> though Davis and Hartman<sup>11</sup> reported that in monkeys almost the entire vaginal epithelium is desquamated prior to the onset of labor.

A smear was examined from a patient three and one-half months pregnant who expelled a hydatidiform mole a week later. It resembled the average cytologic picture of this gestation period. High chorionic gonadotropin levels which in this patient exceeded 200,000 rat units per liter of urine apparently do not directly affect the cytology of the urinary tract.

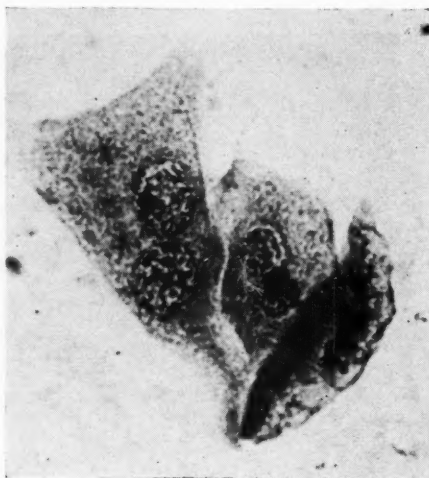


Fig. 7.—Large multinucleated cells obtained on the seventh day prior to the onset of labor. (×600.)

### 3. In Various Other States.—

The cytology of the urinary sediment of prepubertal girls, menopausal women, and adult men and women receiving estrogen therapy was also studied to gain some insight into what might be responsible for the changes observed during pregnancy.

In smears from prepubertal girls cellularity was scanty to moderate, with very little clustering. The cells were small to moderate in size and varied from round or oval to more waferlike in form. Small outer basal cells were evident with vesicular nuclei and small amounts of cytoplasm. Superficial and intermediate cells were more numerous and had central vesicular nuclei and homogeneous cytoplasm. Staining was entirely basophilic.

The cytologic picture of postmenopausal women was rather similar to that of prepubertal girls, though the cytoplasm was less homogeneous and the nuclei were not as vesicular or as large as in the prepubertal smear. Male urines showed only a few scattered cells, round to squamouslike with rather compact nuclei.

Examination of urines from men receiving estrogenic therapy for prostatic carcinoma showed marked changes from the normal male smear, including heavy cellularity, an increase of large superficial cells, pyknosis, eosinophilia, and cytoplasmic granules. Urinary smears from postmenopausal women receiving estrogenic preparations showed similar alterations, but neither of these smear types were confused with those of pregnancy. The most striking difference was the lack of navicular cells and the marked eosinophilia in the smears of those receiving estrogenic hormones.

### Reliability as a Pregnancy Test

After a study of urinary smears from the various sources mentioned, 143 urine specimens were prepared and examined as unknowns and classified as being from pregnant or nonpregnant patients to test the reliability of the urinary smear as a means of detecting pregnancy. Table I gives the results.

Of the five smears from nonpregnant patients classified as those of pregnancy, four were of specimens obtained at the time of the premenstrual phase of the menstrual cycle. The other smear was of a specimen from a woman on the fourteenth day of her cycle. However, her periods were irregular, every three to four weeks, and her urinary smear resembled a premenstrual smear more than the late follicular or postovulatory smears. The fact that five smears from nonpregnant women were classified as from pregnant women seriously detracts from the diagnostic value of this method because false positives could obviously lead to more difficulties than false negatives. Also, it may be seen in Table I that by far the highest percentage of errors in smears of the pregnancy group was in those taken prior to six months; yet this is the period when laboratory tests are most needed for the diagnosis of pregnancy.

TABLE I. RELIABILITY OF URINARY SEDIMENT STUDIES AS A DIAGNOSTIC TEST FOR PREGNANCY

	TOTAL SPECIMENS	NON- PREGNANT	PREGNANT	PREGNANT LESS THAN 6 MONTHS	PREGNANT 6 MONTHS OR MORE
Smears examined	143	66	77	32	45
Smears falsely diagnosed	13	5	8	6	2
Percentage error	9.1	7.6	10.4	18.75	4.4

### Comment

A correlation of the changes in the cytology of the urinary tract with the varying hormonal levels during the menstrual cycle and pregnancy is profitable in that it gives us an insight into hormonal effects on the cytology of the urinary tract and helps explain the unreliability of its study as a means of detecting early pregnancy. Smears taken during the menstrual and early follicular phases of the normal menstrual cycle when hormonal levels are low show few cells. As the estrogen secretion rises, more superficial cells appear; nuclear pyknosis and cytoplasmic granules and vacuolation increase. All these changes in the urinary cytology are known to be associated with administration of this hormone.<sup>2</sup> With the postovulatory fall in estrogen, regression occurs. Then, as both estrogen and progesterone secretion increases, further alterations in the smear are evident, such as enlargement of nuclei, wrinkling, and increased numbers of intermediate cells. With a decrease in both hormones prior to menstruation, the premenstrual smear shows a desquamation of all cell types. Then cells with vesicular nuclei and homogeneous cytoplasm indicative of low hormonal activity appear during the menstrual flow.

Similarly, on examination of the urinary smears of prepubertal and postmenopausal women, as well as men, the criteria indicative of weak stimulation by estrogen and progesterone are revealed. There is a general paucity of cells, but a high percentage of outer basal-cell types and homogeneous cytoplasm with granular to vesicular nuclei even in the superficial and intermediate cells. When smears of men or postmenopausal women receiving estrogen preparations are studied, marked changes are found which must be ascribed to administration of this hormone.

During pregnancy it is likely that the rising estrogen and progesterone production known to occur in this state<sup>12</sup> is responsible for the altered cytology.

Chorionic gonadotropin apparently does not influence the cytology directly because no specific changes were seen in the smear from the case of hydatidiform mole with the high urinary gonadotropin titer. Also Browne and Venning<sup>13</sup> have shown that the peak of gonadotropin excretion is reached during the third month of pregnancy following which it rapidly falls to a low level for the remainder of pregnancy. Yet the most typical cytology was seen in the last trimester of pregnancy.

On the other hand, in early pregnancy estrogen and progesterone production is not greatly increased over the normal menstrual peaks,<sup>12</sup> but it is highest in the last trimester when the cytological changes are most characteristic. This fact offers an explanation for the higher percentage of error in examining unknown smears taken during the first six months of gestation. The question arises as to whether the increased estrogen and progesterone act together or whether one acts alone to cause the altered cytology.

Rakoff, Feo, and Goldstein<sup>14</sup> injected progesterone in doses of 10 mg. into normal adult women and obtained no demonstrable changes in the vaginal smear. Even in larger doses approaching the level of secretion in pregnancy no specific change was observed. However, there is no report of a combination with high doses of estrogen.

The changes that occur in the cytology of the urinary sediment on estrogen administration have been described. They bear some resemblance to the cytology of pregnancy, but differences are evident, particularly in the intermediate cell types. The tendency is for estrogen administration to produce increasing eosinophilia as well as a preponderance of superficial cells, while in the pregnancy smear these two features are not as marked as in the estrogen-treated patients. Also, in the vaginal smear, basophilia increased in the premenstrual phase of the menstrual cycle before estrogen levels began to drop, indicating that the combined effect of estrogen and progesterone on the epithelium of the vaginal and urinary tracts differs from that of estrogen alone. These observations justify the view that the combined action of estrogen and progesterone produces the typical cytology of pregnancy.

The alterations in the urinary smear preceding labor are interesting in view of what is known about hormonal changes at this period. Smith, Smith, and Schiller<sup>15</sup> have reported a gradual fall in estrogen secretion during the last two weeks of pregnancy which becomes precipitous at the onset of labor. Just as the premenstrual smear shows an increased desquamation with the fall in hormone levels, so the apparent desquamation of urinary tract epithelium observed in the last week of pregnancy may well be due to a gradual fall in estrogen beginning about two weeks before term and, as the estrogen falls precipitously at the onset of labor, so does the shedding of the epithelium of the urinary tract increase. Whatever the hormonal change, the findings in the urinary smear seem to indicate that some alteration in hormonal balance precedes and accompanies the onset of labor.

This study demonstrates that the cytology of the urinary sediment responds to the hormonal variations of women in a characteristic manner. Because the changes in the urinary cytology parallel the shifts in hormonal secretions during the gestation period, they do not offer a reliable method for detecting early pregnancy when hormonal production does not exceed the menstrual peaks. Yet the freedom of the urinary smear from mucus, infection, blood, bacteria, and other obscuring conditions seen in vaginal smears suggests its value as a more accurate means of determining hormonal activity in women. For example, Fletcher<sup>16</sup> reported the presence of characteristic changes such as the appearance of the so-called postpartum cell in the vaginal smear of patients with



abortions. In a suspected abortion, the urinary smear might well be of value in diagnosis, since similar changes would be expected. While the vaginal cytology would be obscured by the bleeding likely to be present and the taking of such a smear would introduce a possible source of contamination into the genital tract, the urinary smear would have neither of these disadvantages. Similarly, the cytological changes during the menstrual cycle might be of value in determining the presence or absence of the progestational phase. This information is of importance in sterility studies, since presence of such a phase is considered evidence of ovulation in the cycle.<sup>17</sup> The possibilities of using the urinary smear as an aid to diagnosis is being further explored.

### Summary

The sediment of catheterized urine was stained and its cytology was studied with reference to changes during pregnancy and the menstrual cycle. Specimens were obtained from all stages of pregnancy, from men, prepubertal girls, normally menstruating and postmenopausal women, and from patients receiving estrogen therapy.

Cytology was found to vary with estrogen and progesterone levels. Thus cyclical variations were seen during the menstrual cycle. Smears from subjects with low hormonal levels showed many small round cells, deeply basophilic and with vesicular nuclei. Indications of estrogenic stimulation were increased cellularity, eosinophilia, nuclear pyknosis, cytoplasmic granules, and vacuolation.

Pregnancy smears exhibited changes during the various stages of the gestation period and were consistently diagnostic in the latter half only when estrogen and progesterone levels are highest. Typical cytology included evidences of estrogenic stimulation and groups of cells with heavy contours, pyknotic nuclei, and vacuolated cytoplasm. In the week preceding labor, alterations were observed which consisted of increased desquamation and the appearance of cells with deeply staining cytoplasm and large vesicular nuclei.

When the examination of the urinary sediment was used as means of diagnosing pregnancy, an accuracy of 90.9 per cent was achieved in 143 unknown specimens. However, in smears from pregnancies earlier than six months, correct diagnosis was made in only 81.25 per cent. Though the changes in urinary cytology were unreliable in diagnosing early pregnancy, it is believed their study may offer a means of detecting certain hormonal variations in women.

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4200 EAST NINTH AVENUE

## A METHOD OF URETEROINTESTINAL ANASTOMOSIS ADAPTED TO PELVIC SURGERY\*

### Preliminary Report

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IN THE solution of major pelvic surgical problems in the operating room, diversion of the urinary stream is often important and necessary. This is particularly true in patients previously subjected to irradiation and in those who have sustained severe ureteral damage at or following a previous operation. With the present trend toward radical pelvic surgery in some cases of carcinoma of the cervix, local recurrences after radium and x-ray therapy, and even in some cases of advanced neoplastic disease in the pelvis, frequent occasion will arise for implantation of the ureters into the bowel (Fig. 1). The degree of success of a ureterointestinal anastomosis will depend on the prevention of immediate leakage, the avoidance of undue ureteral constriction, immediate and latent, with its resultant hydronephrosis and other complications, and the initiation and maintenance of a valvelike new sphincter to prevent reflux and consequent ascending infection.

Of the several available techniques, the Coffey I and the Coffey II are the most popular, but have definite disadvantages. In the Coffey I method, the more satisfactory of the two, the ureter is buried in the musculature of the bowel for a short distance and then drawn into the bowel by means of an anchoring suture. This procedure, especially when a ureter has been compromised by radiation or stripped of too much periureteral blood supply, gives rise to a dangerous situation which may permit infection to follow along the trough, or eventuate in necrosis of the ureter. In this type of implantation there is also danger of edema of the bowel causing subsequent ureteral compression. The Coffey II differs from the Coffey I method only by the additional introduction of ureteral catheters and leaving them in situ until postoperative edema has subsided. This method has lost popularity, chiefly because of the increased danger of ascending infection. Obviously, the Coffey III, the Higgins and the Jewett techniques, all multiple-stage operations, are not applicable when both ureters must be transplanted immediately and the bladder removed as a single procedure.

It, therefore, seemed desirable to devise a method whereby the following advantages and objectives might be achieved: (1) a minimum consumption of operating time; (2) a generous blood supply to the ureter, particularly

\*Presented by invitation, at a meeting of the New England Obstetrical and Gynecological Society, May 4, 1949; also at a meeting of the New York Obstetrical Society.

where the ureter may have been irradiated or stripped of its periureteral tissue, the latter often being necessary when dealing with malignancy; (3) less damage to the bowel, thus decreasing the likelihood of edema and infection; (4) reduction in the number of necessary sutures; (5) an increase in the length of the ureteral stoma in the intestinal lumen which is not sutured to the bowel wall, thus providing a more efficient valvelike action for the ureter within the bowel; (6) facilitation of immediate output of urine in contrast to the twenty-four to forty-eight hour period of anuria which so often occurs after the Coffey operation; (7) applicability to a high intraperitoneal or retroperitoneal anastomosis, since this tends to lessen the infection; and (8) adaptability to simultaneous bilateral ureterointestinal anastomosis and total cystectomy.

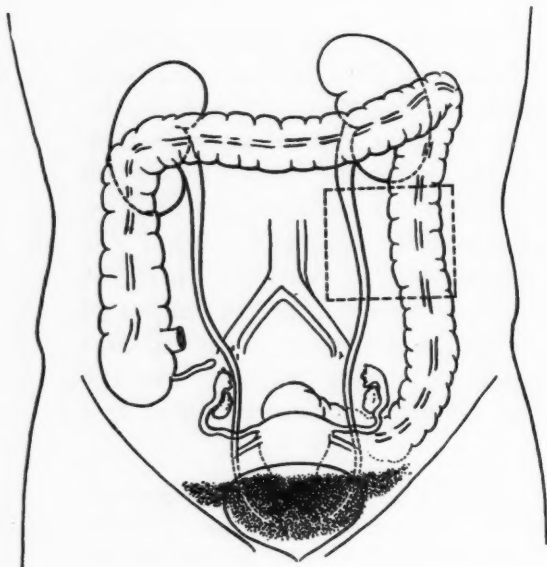


Fig. 1.

Fig. 1.—Extensive carcinomatous involvement of the pelvis, showing ureter-colon relationship above.

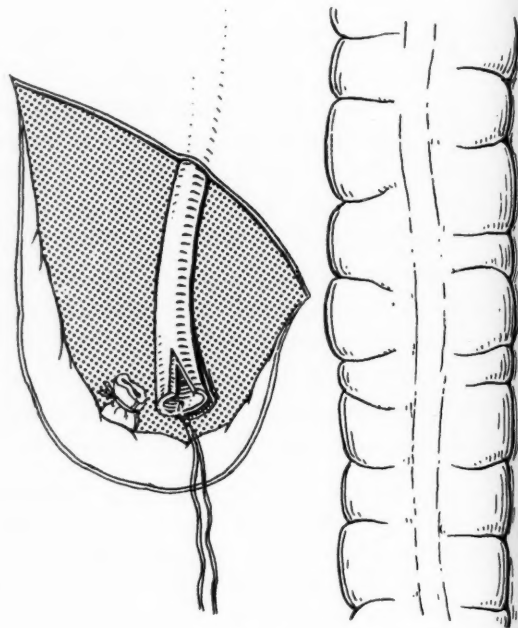


Fig. 2.

Fig. 2.—Cut end of ureter prepared for implantation.

It is often presumptuous to claim originality for anything in the field of medicine and surgery, since many old methods, procedures and details are so often rediscovered. At least sixty different operations for ureterointestinal anastomosis have been described. Davalos<sup>1</sup> called attention to the fact that a transverse incision in the wall of the rectosigmoid causes less damage to the blood supply than a longitudinal one, and anastomosed the ureters in the bowel after elevating a flap of peritoneal and muscular tissue. This procedure was carried out in seventeen dogs and four patients. Recently, Schinagel<sup>2</sup> described a technique of implantation by tunneling between the muscularis and the mucosa, which he had used in four dogs. I can only say that I have been unable to find anywhere in the literature a description of the following technique which I have now utilized in seven cases.



### Method

1. The mobilized ureter is allowed to approximate the posterior serosal surface of the bowel into which it is to be implanted.

2. The cut end of the ureter is prepared by making a 0.5 cm. nick on the antiperitoneal side. A fine suture is then placed opposite this split on the peritoneal side to be used later for traction (Fig. 2).

3. A pair of Babcock clamps are placed on the bowel 2 cm. above the lower end of the ureter and a second pair placed 3 to 5 cm. above the first one (Fig. 3). At each of the points where the clamps are placed a 1 cm. transverse slit is made in the visceral serosa (Fig. 4).

4. A glass rod or straight blunt tip clamp is then gently insinuated under the serous coat of the bowel from the superior to the inferior slit, or vice versa (Fig. 5). Care should be taken so that this is not placed near the taenia of the bowel. Fine blood vessels will then be seen coursing through the serosal layer between the bowel and the glass rod.

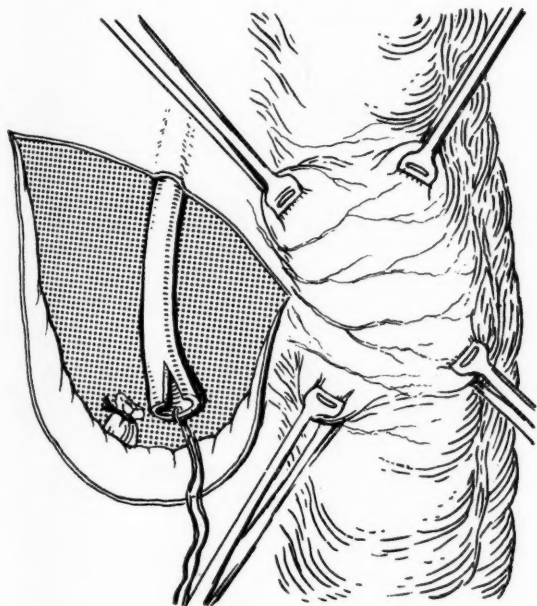


Fig. 3.

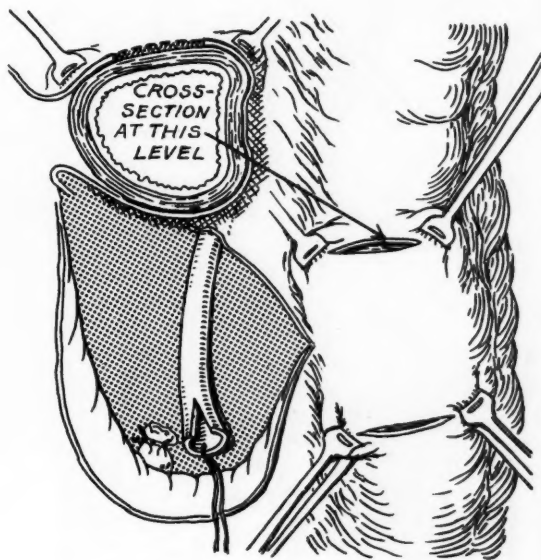


Fig. 4.

Fig. 3.—Babcock clamps placed on the bowel.

Fig. 4.—Upper and lower transverse slits in the bowel serosa.

5. The glass rod is then withdrawn and a straight clamp inserted through the newly created channel. The suture in the end of the ureter is grasped in the jaws of the clamp and the ureter drawn through this sleeve (Fig. 6). The apposition of the ureter to the sleeve should be such that approximately 2 cm. of the ureter projects below the lower end.

6. Fine sutures are then placed at each of the four angles of the new canal, attaching the peritoneal surface of the ureter to the serosal and subserosal tissues of the bowel, thus closing the sleeve. (In an alternate method only the superior sutures are inserted and the lower angles of the sleeve are not closed until the ureter has been placed within the lumen of the bowel.) (Fig. 7.)

7. A sliding flap of peritoneum may be brought over to protect the upper part of the sleeve (Fig. 8).

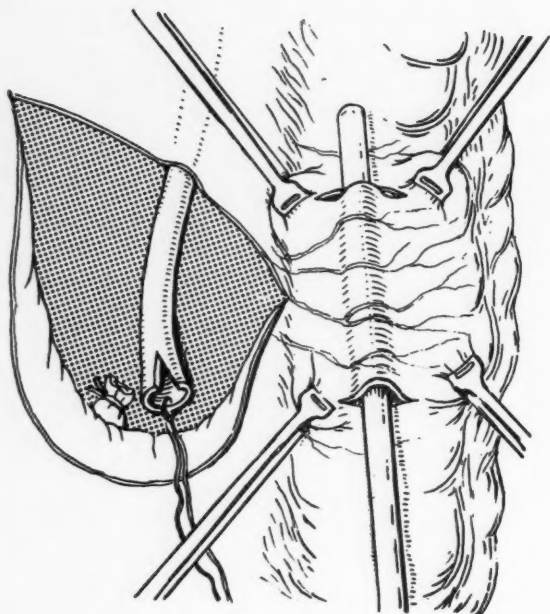


Fig. 5.

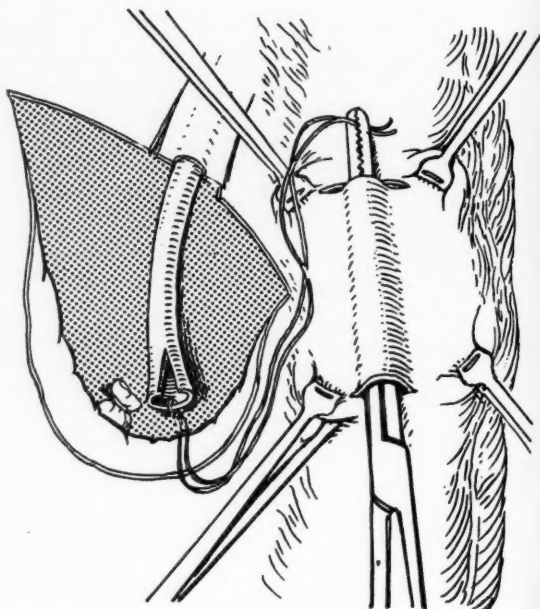


Fig. 6.

Fig. 5.—Glass rod insinuated into new channel leaving blood vessels above.  
Fig. 6.—Glass rod replaced by straight clamp.

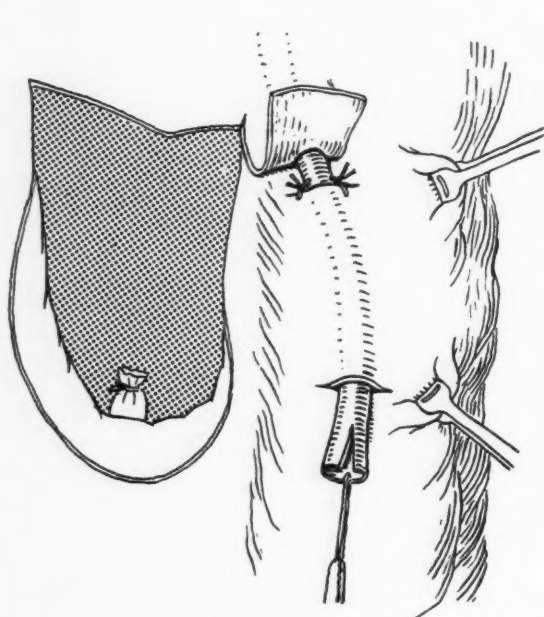


Fig. 7.

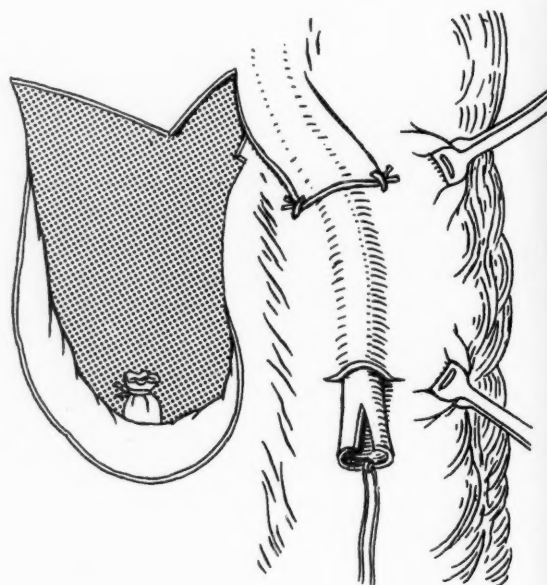


Fig. 8.

Fig. 7.—Sutures closing upper end of the sleeve.  
Fig. 8.—Sutures tied.

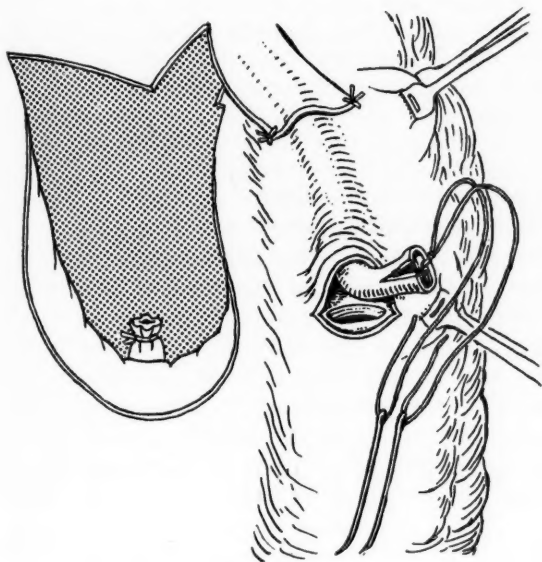


Fig. 9.

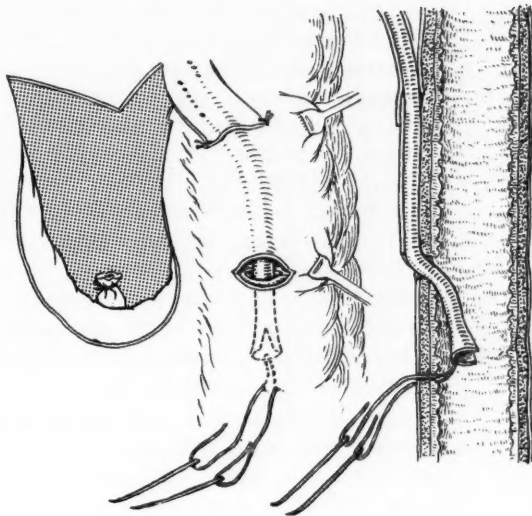


Fig. 10.

Fig. 9.—Small incision made through all coats of the bowel.  
Fig. 10.—Ureter completely within the bowel lumen.

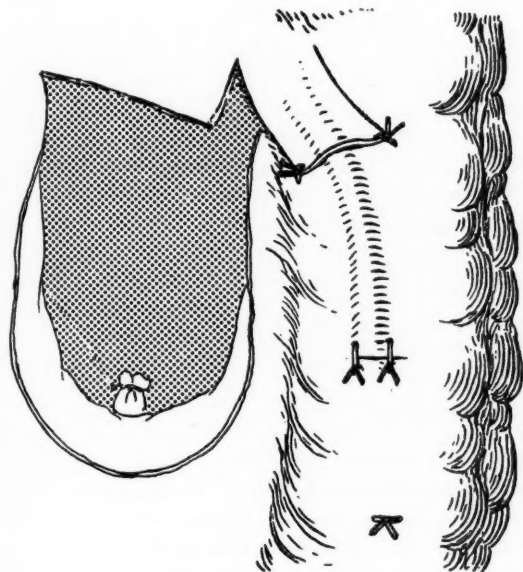


Fig. 11.

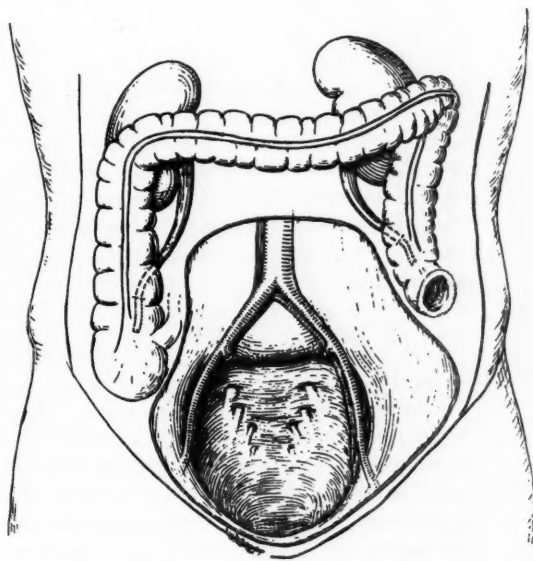


Fig. 12.

Fig. 11.—Operation completed.  
Fig. 12.—Showing adaptation to implantation in either the ascending or descending colon.

8. Directly below the end of the sleeve a small incision is made obliquely through the circular muscular coat. A small puncture is then made through the bowel mucosa and 1 to 2 cm. of the ureter inserted into the bowel (Figs. 9 and 10). This small incision at the inferior end of the sleeve is then closed with fine chromic catgut and an overlying layer of silk sutures. A small piece of omentum may be placed over the second layer of suture for protection. In the alternate method, the lower angle of the sleeve is retracted, and the small incision through the circular muscular coat and the puncture through the bowel mucosa are made just above the lower limit of the sleeve, before insertion into the bowel (Fig. 10). Several fine sutures are used to approximate the ureter to the opening in the bowel and the lower angle of the sleeve is then closed (Fig. 11).

9. The bowel is then allowed to fall into position. Should the implant of the right ureter be into the cecum or the ascending colon, the implant will automatically fall retroperitoneally (Fig. 12). On the left side the ureter in the descending colon will also readily adjust itself retroperitoneally. Should it be placed in a colostomy, a more lateral and extraperitoneal placement may be obtained by bringing the ureter through the bowel mesentery.

10. While it was not found necessary in two cases, in the others a small rubber-tissue wick was sutured to the bowel with fine plain catgut and brought out through a lateral stab wound, thus giving the added protection of drainage to the site of the anastomosis.

I have now done this operation, which was devised in February, 1948, on seven patients, and it has seemed to fulfill its objectives perfectly in all of them.

### Case Reports

CASE 1.—This was a patient with a Stage IV adenoacanthoma of the cervix, whose chief complaints were agonizing pelvic pain, nausea, and vomiting, and abdominal distention, following 20,000 r. units of roentgen irradiation, plus vaginal cone and radium therapy. The patient had a severe anemia and blood urea nitrogen of 28.2. At operation, the ureters were found completely encased in radiation fibrosis, and had to be stripped for a distance of 15 cm. to permit a pelvic viscerectomy. The right ureter was anastomosed with the cecum and the left with the descending colon, followed by a colostomy. Urinary drainage from the stoma started promptly and continued satisfactorily, blood urea nitrogen dropped to 13 by the seventh day, and the average postoperative temperature was less than 100° F. Unfortunately, the patient died suddenly on the ninth postoperative day from pulmonary embolus. At autopsy, both ureterocolonic anastomoses were found to be perfectly healed and intact.

CASE 2.—This patient had a Stage IV postradiation epidermoid carcinoma of the cervix. Two pregnancies had been terminated 10 to 20 years previously, respectively, because of uremia, and a thyroidectomy for thyrotoxicosis had been done two years before. Intravenous urograms showed normal renal function on the right side, but a nonfunctioning kidney on the left. Operation disclosed a double ureter with hydronephrosis on the left side, but no evidence of radiation damage. There was a considerable gush of urine when the ureter was severed above the point of obstruction in the pelvis. A radical hysterectomy, cystectomy, vaginectomy, and extensive lymph node dissection were done, followed by implantation of the left ureter into the sigmoid and the right into the cecum. Urinary output was 2,800 c.c. on the first postoperative day, and continued profusely, until the eighth day, when the patient developed edema of the extremities and an electrocardiogram showed evidence of myocardial damage. Despite digitalis and oxygen therapy and blood plasma given in an effort to raise the serum protein, which had fallen to 4.2, the patient expired on the thirteenth day and permission was obtained for only a partial autopsy. The cause of death could not be found within the abdomen, and the ureterointestinal anastomoses were found in perfect condition.



CASE 3.—This patient had a previously untreated Stage IV, Grade II, epidermoid carcinoma of the cervix, so extensive that the cervix had been completely destroyed, the vaginal vault was deeply invaded, and the tumor involved the base of the bladder. Radical hysterectomy, total cystectomy, and transplantation of both ureters into the sigmoid, were followed by a free urinary output, a reduction in blood urea nitrogen, and a smooth convalescence. Intravenous urograms after the patient's discharge from the hospital showed moderate hydronephrosis but good bilateral renal function, and she is now in excellent condition, free from complaints.

CASE 4.—This patient had a transitional-cell carcinoma of the cervix, previously treated elsewhere, with constant pelvic pain, severe radiation reaction and slough of the abdominal skin, and a vesicovaginal fistula. After a thorough preoperative study, including liver function tests, biopsies of inguinal lymph nodes, punch biopsy of the liver, and pyelograms, a radical pelvic viscerectomy was done with bilateral implantation of the ureters into the cecum and sigmoid, respectively. This patient eventually died on the sixty-third postoperative day of unexplained causes. At autopsy, the ureterointestinal anastomoses were found in perfect condition.

CASE 5.—This patient had had a supracervical hysterectomy in 1942, followed by a Grade III carcinoma of the cervical stump with metastasis to the regional nodes, causing lymph and circulatory stasis in the right lower extremity, in August, 1947. She was given x-ray and radium irradiation, and intravenous procaine, but the pelvic pain became persistently worse. X-ray studies showed bone metastasis of the right pelvic wall, and a moderate hydronephrosis on the right side, but no remote metastases. At operation, the tumor mass was found to involve the cervical stump, the right half of the bladder, the right tube and ovary, and the right pelvic wall en masse. The right ureter was imprisoned in neoplastic tissue and dilated to 3 cm. At operation, the right tube and ovary and two thirds of the bladder were resected, with ligation of the hypogastric vessels and a high resection and colonic implantation of the right ureter. The left ureter was not disturbed, and still functions into the revised bladder. The patient was discharged from the hospital on the twentieth postoperative day, with a good appetite, complete relief from pain, and emunctories functioning well. She has now gained in weight and is being given further roentgen therapy.

CASE 6.—This patient had a Stage IV epidermoid carcinoma of the cervix that proved highly resistant to an intensive course of irradiation, which was given in 1946 and 1947. There was a deep crater involving all of the vaginal vault and extending into the parametrial areas as well as the uterus, and a nodular induration into the right broad ligament and base of the bladder. Biopsies revealed epidermoid carcinoma with no evidence of radiation reaction. A radical operation was done in February, 1948, including radical lymph node dissection and hysterectomy, total cystectomy, vaginectomy, and partial excision of the right hypogastric vein, with right ureteroappendicocostomy and left ureterosigmoidostomy. The patient left the hospital on the twentieth postoperative day with the ureteral anastomoses functioning well, and later returned to Sweden.

CASE 7.—This patient had received extensive x-ray and radium therapy for an epidermoid Grade II carcinoma of the cervix. One year later there was recurrence of pain and bleeding. X-ray therapy was again started and then discontinued. She was given large doses of opiates with little control of pain. Examination revealed radiation slough and a tumor involving the vaginal vault, with fixation of both broad ligaments. Radical hysterectomy, with contiguous node dissection, total cystectomy, vaginectomy, right ureterocecal anastomosis and left ureterosigmoidal anastomosis were done. The postoperative course was uneventful; average temperature range 99.2° F. urinary output the first twenty-four hours 1,735 c.c. By the fourth postoperative day the output was 3,400 c.c. Blood urea nitrogen on the eighteenth postoperative day was 15 mg. per cent. The patient was discharged from the hospital with only some difficulty with rectal sphincter control.

Most of the details of the preoperative study and preparation, general operative technique, postoperative treatment, and follow-up observations in these seven cases have been omitted for the sake of brevity. Likewise, the indications for, and relative merits of, extremely radical surgery in cases of advanced malignant disease in the pelvis are not part of the subject under discussion. However, it may be just as well that my first opportunities to utilize this new method of ureterointestinal anastomosis have been in such cases, since the autopsies, two complete and one partial, afforded ample opportunity to inspect the anatomical end results, and the other four patients who were discharged from the hospital alive have demonstrated the functional capacity of the method.

### Summary

A new method of ureterointestinal anastomosis is presented:

1. It is readily applicable to intra- or retroperitoneal ureterointestinal anastomosis, particularly to tissues that have been irradiated.
2. It provides an adequate blood supply to the ureter and minimizes damage to the bowel, which should result in a better ureterointestinal anastomosis, and one that is less likely to result in constriction with subsequent hydro-ureter and nephrosis than other methods.
3. It promotes immediate output of urine with relatively low blood urea nitrogen, probably because of lessening of the edema about the site of anastomosis.
4. It reduces the incidence of infection about the site of ureterointestinal anastomosis.
5. Either fixation or nonfixation of the ureteral stoma may be used, but the latter seems preferable.
6. The operation is relatively simple, can be done rapidly, and provides a promptly functioning anastomosis, free from the danger of leakage. While the method has so far been used in only extremely poor-risk patients, all have done well from the urological standpoint, i.e., ureterointestinal anastomosis.
7. The method is equally applicable to better-risk patients, who may require diversion of the urinary stream, i.e., and expedient ureterointestinal anastomosis. (Experimental work on this type of ureterointestinal anastomosis carried out on four dogs by the author fulfills the requirements of a successful anastomosis.)

Since the completion of this paper, I have done this operation on six additional patients, four of whom are living.

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580 PARK AVENUE.

## HERNIA OF DOUGLAS' POUCH AND HIGH RECTOCELE\*

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IT IS often difficult to determine by vaginal inspection and palpation whether a bulging of the upper posterior vaginal wall is caused by hernia of Douglas' pouch, commonly called enterocele, or by high rectocele. These two conditions usually have one point in common. They are both hernias and, excepting a rare type of the cul-de-sac hernia, they develop in the same manner, that is, through a defect in the musculofascial structure of the upper posterior vaginal wall. Etiologically, however, the two conditions are quite different. They may and frequently do occur simultaneously.

The rare variety of hernia of Douglas' pouch may be found without the presence of gross defect in the posterior vaginal wall, and is due most likely to congenital prolongation or extension of the cul-de-sac peritoneum downward and forward in the loose cellular tissue space between the vaginal and rectal fascial layers. It may extend as far as the perineum.

The usual variety of hernia of Douglas' pouch appears because of impairment of the structure of the upper posterior vaginal wall, and, while it may be that this impairment is congenital, it is usually the result of childbirth trauma.

High rectocele occurs also because of weakness of the upper posterior vaginal musculofascial structure, but in addition there is usually a weakness or defect in the musculofascial structure of the anterior rectal wall at or near the same point. Here again, while one must admit that these defects could be congenital, they are in practically all instances acquired through trauma incident to childbirth.

Prolapse of the uterus will increase the relaxation of the vaginal wall and will therefore contribute to the development of these hernias into the vagina.

Inadequate repair, such as low colporrhaphy and perineorrhaphy, in these cases of upper posterior vaginal hernia, will result in advance of the hernia as an ever-enlarging pouch which will roll down over the high point of the repair.

By far the most commonly neglected step in vaginal plastic procedure is reconstruction of the upper posterior vagina. Cystocele and urethrocele or the incontinent sphincter may be repaired indifferently, but some attempt at correction is made. Perineorrhaphy is nearly always done and usually with it is combined some degree of posterior colporrhaphy. Unfortunately, however, the upper posterior vagina is more often overlooked entirely or neglected because "it doesn't look too bad." This accounts for large numbers of so-called recurrences of vaginal prolapse, rectoceles, enteroceles, and vault prolapses which follow vaginal hysterectomy, abdominal hysterectomy, the Manchester operation, or other vaginal plastic operations. Cystocele, urethrocele, and urinary incon-

\*Presented at a meeting of the Pacific Northwest Obstetrical and Gynecological Association, Portland, Oregon, April 28, 1949.

tinence may recur if poorly repaired but not ordinarily because they have been overlooked. The one exception to this is, of course, when abdominal hysterectomy is performed without recognition of the need for vaginal repair.

The purpose of this paper is to stress the necessity of recognition of hernia of Douglas' pouch and/or high rectocele, to stress also the importance of repair of the upper posterior vaginal wall, and to suggest methods of repair in the course of ordinary vaginal plastic procedures, or after vaginal hysterectomy, or in the presence of vault prolapse.

### Anatomy

The important features in the anatomy to be considered in correction of hernia of Douglas' pouch and/or high rectocele are the supporting structures of the upper vagina and the adjacent rectum and the relationship of the pouch of Douglas to them.

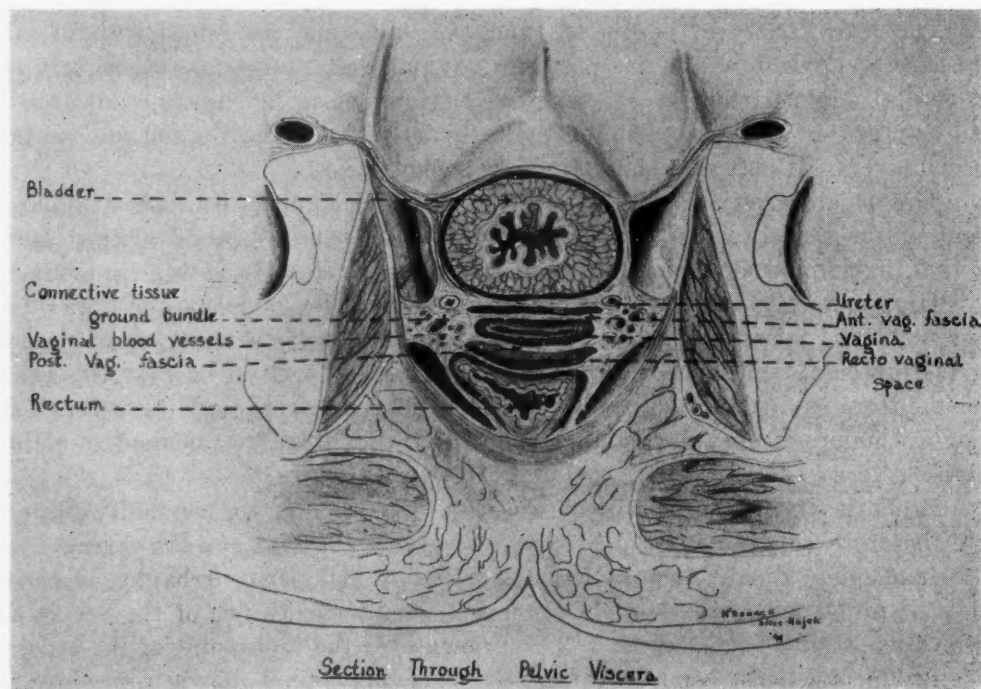


Fig. 1.

Let us first recall without elaborate detail the fibrous tissue which is to be found in this region. This fibrous tissue is variously designated visceral endopelvic fascia, fibrous connective tissue, connective tissue ground bundle, vaginal and rectal fascial capsules, etc. Uhlenhuth, Day, Smith, and Middleton of Baltimore have published in *Surgery, Gynecology and Obstetrics*, for January, 1948, a most excellent work on dissection of the visceral endopelvic fascia and particularly that portion known as the hypogastric sheath. They point out the difference in origin and structure of the horizontal ground bundle and the hypogastric sheath and stress the important roles they play in supporting and mooring the pelvic viscera.



Broadly speaking, the visceral portion of the endopelvic fascia leaves the lateral pelvic wall where it is inserted along the iliopectineal or white line. At this point it is continuous with the parietal portion of the endopelvic fascia and particularly with that part which covers the levator diaphragm. It stretches medially as a broad thick sheet of aponeurotic fibrous tissue which splits into three layers to envelop the visceral contents of the pelvis—the bladder, the vagina and cervix, and the rectum. The ventral layer divides to pass behind and in front of the bladder and fuses with its counterpart on the opposite side.

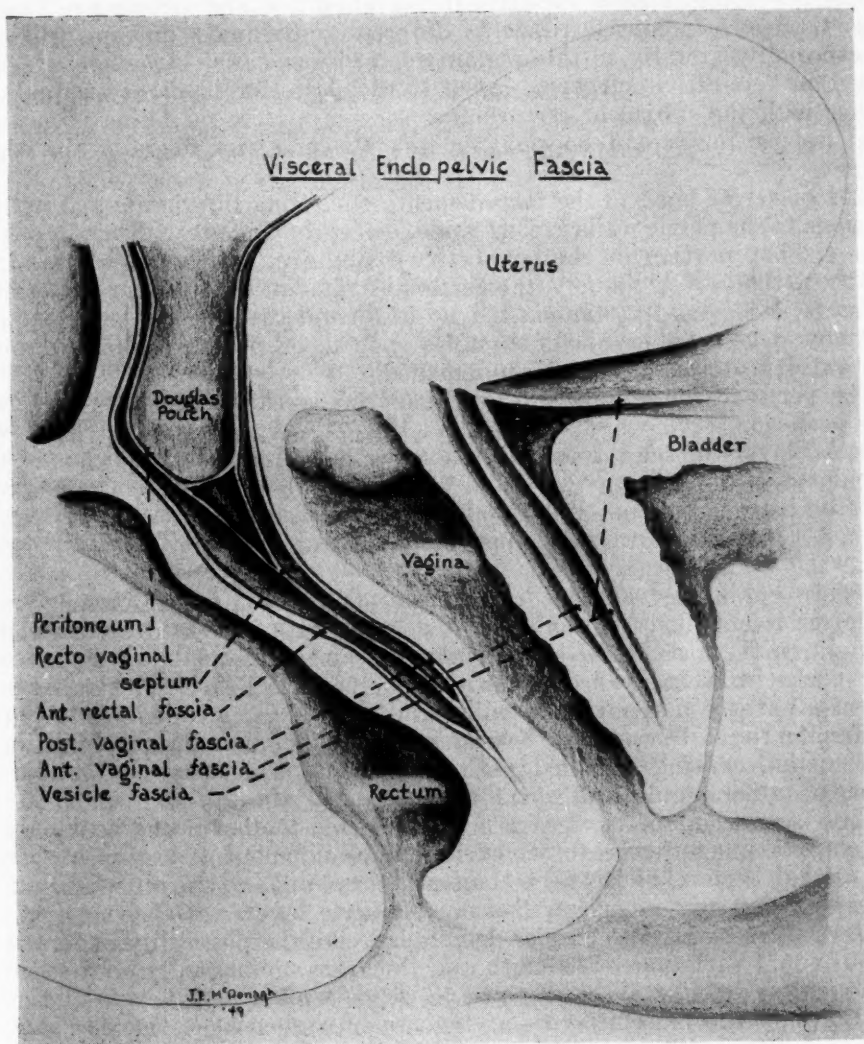


Fig. 2.

The dorsal layer similarly ensheathes the rectum and the median layer envelops the vagina, its cranial part being fused centrally to the cervix and laterally to the cardinal ligaments of the uterus which form the base of the vertical portion of the connective tissue ground bundle. The latter is referred to by Uhlenthuth and associates as the hypogastric sheath.

These fibrous connective tissue layers and capsules of the pelvic viscera contain the blood vessels, lymphatics, and nerves supplying the pelvic viscera.

About the main trunks of supply, and particularly the venous channels, the connective tissue is condensed and strong. It is this perivascular condensation of connective tissue about the uterine vessels which is chiefly responsible for the supporting strength of the cardinal ligaments.

Just caudal to the cardinal ligament the vaginal arteries and veins traverse the horizontal connective tissue ground bundle between the obliterated hypogastric artery and the upper vagina. Here, too, the fibrous tissue is more abundant and contributes greatly to the support of the vaginal vault (Fig. 1).

There is a well-known variation in concentration and strength of fascial or fibrous tissue, as in muscle tissue in different individuals, but one will always find, especially laterally in this region, good fibrous tissue structure which may be used in reparative surgery. Also, if the posterior layer of vaginal fascia together with the subjacent rectovaginal septum and rectal fascia is not strong enough to use for repair, one may include the posterior fibers of the cardinal ligament.

The posterior layer of the fascial sheath encircling the vagina and its lateral extensions to the pelvic walls are, as noted above, continuous with the hypogastric sheath or that portion of the connective tissue ground bundle which attaches medially to the cervix, namely, the cardinal ligament. This upper posterior vaginal fascia is frequently traumatized by labor and through the resultant defect there may develop a hernia of Douglas' pouch, or protrusion of the anterior rectal wall if its fascia has also been damaged.

The peritoneal cul-de-sac of Douglas normally extends about 1 inch caudal to the posterior cervicovaginal junction (Fig. 2). At this point it lies between the fascial layers of the vaginal and rectal walls. From its tip downward to the perineum and laterally to the pelvic walls spreads a thin membranous layer interposed between vaginal and rectal fasciae which is known as the rectovaginal septum. It is derived probably from the peritoneum and the fibrous hypogastric sheath.

Where cul-de-sac relationships are normal, herniation through a vaginal wall defect is not likely, although it is possible with increased intra-abdominal pressure. In the instance of a congenitally deep cul-de-sac, however, herniation of the pocket may easily occur and will increase with intra-abdominal strain. Rare cases have been reported in which the pouch has extended caudally in the loose areolar tissue between the fascial layers of the vaginal and rectal walls to the perineum, causing so-called perineal hernia. This may be found in the presence of intact vaginal and rectal walls.

The visceral endopelvic fascial layers referred to above constitute only part of the supporting structure involved in the development of hernia of Douglas' pouch or high rectocele. Between the fascial capsules and the mucosal linings of both vagina and rectum are well-defined muscle layers. Deficiencies of these muscular layers along with fascial defects increase the possibility of hernia.

Individual variation in strength and thickness undoubtedly occurs here too, and congenital defect may be responsible for development of hernia of Douglas' pouch through the muscle layers of the upper vagina when the fascial wall is also weak. High rectocele may occur similarly when the muscular and fascial coats of the rectum are deficient.

The uterosacral ligaments are peritoneal folds containing smooth-muscle fibers continuous with uterine muscle plus variable fibrous tissue elements. They form the superior borders of the lateral walls of Douglas' pouch, curving backward from the sides of the cervix at the level of the internal os to the posterior pelvic wall at each side of the rectum.

### Treatment

Descriptions in the literature of operations for the cure or prevention of hernia of Douglas' pouch invariably suggest that these ligaments be sutured to-

gether as far back toward the rectum as possible. This is supposed to obliterate the space through which hernia might appear or recur. Another suggestion is that, vaginally or preferably abdominally, successive purse-string sutures be placed in the peritoneal pouch to obliterate it.

Neither of these procedures will cure or prevent high rectocele. Also, in many instances the uterosacral ligaments are little more than reduplications of peritoneum and would not offer good support. In the case of vault prolapse following hysterectomy it may be impossible to locate any vestige of these ligaments. Vaginally it is not always easy to suture them together for any appreciable distance. Two or three sutures will not necessarily prevent hernia of Douglas' pouch, and, on the other hand, if they be united well back to the rectum, the normal function of that organ may be embarrassed.

It would seem more logical to rebuild or repair the structures which are deficient or have been damaged and in so doing one would expect the final result to conform more closely to the normal state.

### Operation

The mucocutaneous junction at the anterior border of the perineum is excised with curved scissors. The posterior vaginal wall is dissected free in the mid-line with blunt-pointed curved scissors keeping as close to the mucosa as possible. The freed portion is divided in the mid-line as dissection proceeds until the cervix or vault is reached. The incisional margins are held in pairs of Allis forceps placed about one inch apart. With a sharp scalpel and finger gauze, beginning at the perineum, all musculofascial tissue is dissected free from the vaginal mucosa on either side right to the junction of posterior vaginal wall and cervix.

At the vaginal vault this dissection is carried as far laterally as is necessary to liberate all damaged or redundant musculofascial structure. This will also expose the more intact lateral portions of these layers which may then be used as much stronger supporting structure in repair (Fig. 3).

The pouch of Douglas is now opened if the presence of a hernial sac is known or suspected and its extent is determined. A moist taped sponge is inserted to push up and protect loops of bowel or omentum and with a finger inside as a guide all redundant peritoneum is dissected free with scissors and gauze. A plain catgut purse-string suture is placed high inside the base of the sac, care being taken to pick up only peritoneum laterally and posteriorly. Anteriorly, the suture may bite into the posterior wall of the cervix at any desired level. The sponge is removed and the purse string is tied while a finger keeps the sac's contents out of the way. The caudal portion of the sac is excised, and from this point on repair of the upper posterior vaginal wall is carried out in the same manner, whether the hernia has originated from Douglas' pouch or anterior rectal wall or from both.

The posterior lip of the cervix is held forward and the mucosal flaps at the vault are held well apart. Two fingers are placed high in the vagina to hold back the rectum and to expose the overlying musculofascial layers, and the crown suture of the posterior vaginal wall repair is inserted (Fig. 4). Chromic catgut No. 1 on a round needle is passed through the musculofascial layers of the upper posterior vagina as far laterally and as high as possible. The posterior borders of the adjacent cardinal ligaments of the uterus may be included in this suture if additional support is required. Beginning on the operator's right, the needle picks up in successive small but definite "bites" all the tissue dissected from the vaginal mucosa across the vault. The needle is then passed back to the right through the posterior wall of the cervix just above the cervicovaginal junction.

This crown suture when tied makes fast to the cervix a ring of plicated (and therefore strengthened) musculofascial tissue. It simply restores torn supports



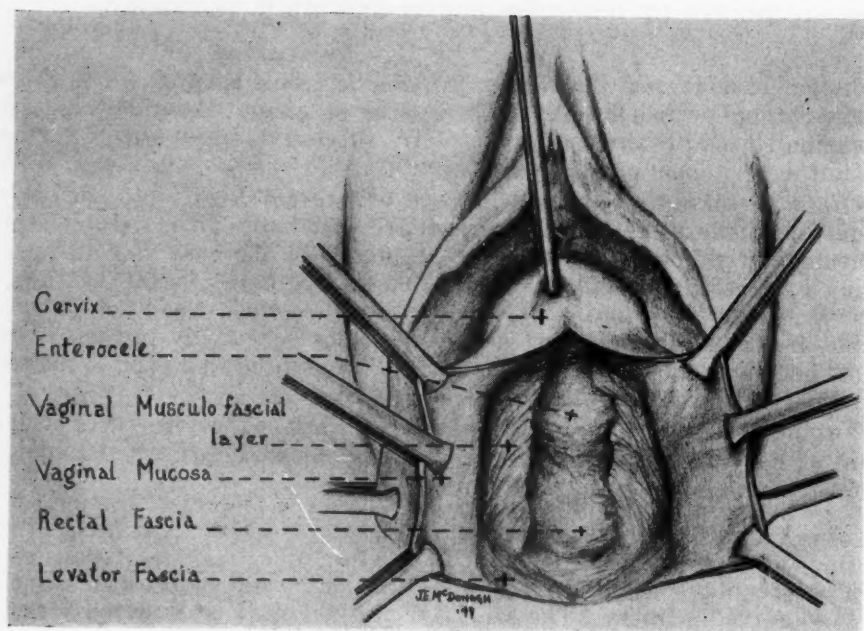


Fig. 3.

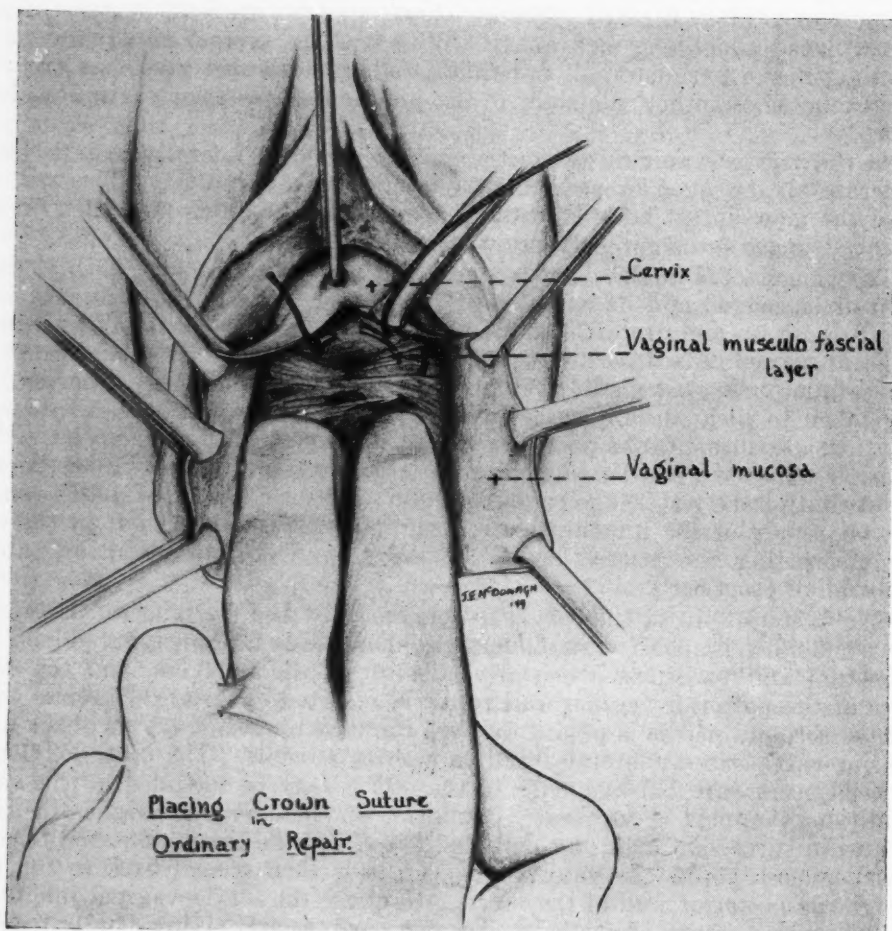


Fig. 4.



to their original position or strengthens deficient structure in its normal relationship. The suture is continued caudal, applying the same principle of plication of all redundant tissue to the weakened supporting structure of the posterior vaginal wall (Fig. 5). The use of continuous suture here tends to "bunch" the thinned-out tissues together and so increase their strength. Shortening of the vagina should not occur because the upper end of the suture is fastened to the cervix which should be fixed at a high level if prolapse is present, i.e., fixation by some such method as in the Fothergill operation for shortening cardinal ligaments.

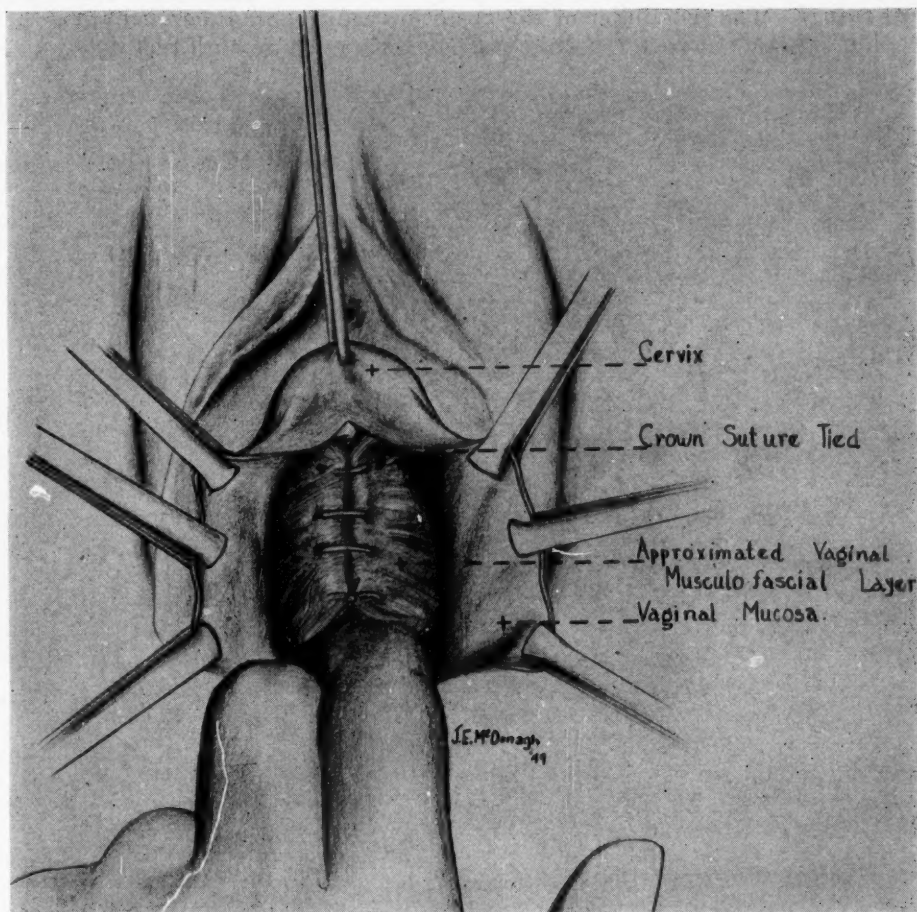


Fig. 5.

In the lower one-half or one-third of the vagina, interrupted sutures are employed to unite the levator fascia and perineal muscles. Excess mucosal flaps are trimmed and the margins are sutured together with a continuous locked stitch of chromic catgut No. 0, beginning at the cervix. This suture picks up small "bites" of underlying fascia to obliterate dead space and fix the mucosa to the fascia. Perineorrhaphy is completed with subcuticular chromic catgut.

When vaginal hysterectomy is done a much better exposure for the dissection and repair of hernia of Douglas' pouch is possible. The sac is closed with a purse-string suture which in this instance begins and ends at the vesicouterine peritoneal flap, includes the peritoneal covering of the inner aspect of all the

uterine ligament stumps and picks up the cul-de-sac peritoneum at a high level. After the upper and lower broad ligament stumps with the uterosacral stumps have been united on each side and to their counterparts on the opposite side, the upper stumps are sutured firmly to the subpubic tissue at the level of the bladder neck. Before the anterior vaginal wall is completely closed, a suture of No. 1 chromic catgut is passed through the uterosacral ligaments or the adjacent cardinal ligaments where they have been drawn together to form the posterior portion of the new pelvic floor (Fig. 6). This suture is held long until the posterior vaginal wall has been prepared as described previously and then it is passed through the musculofascial layers at the vault in like manner and tied as the crown suture. The remainder of the posterior wall repair is carried out as in the foregoing, whether it be for hernia of Douglas' pouch or high rectocele.

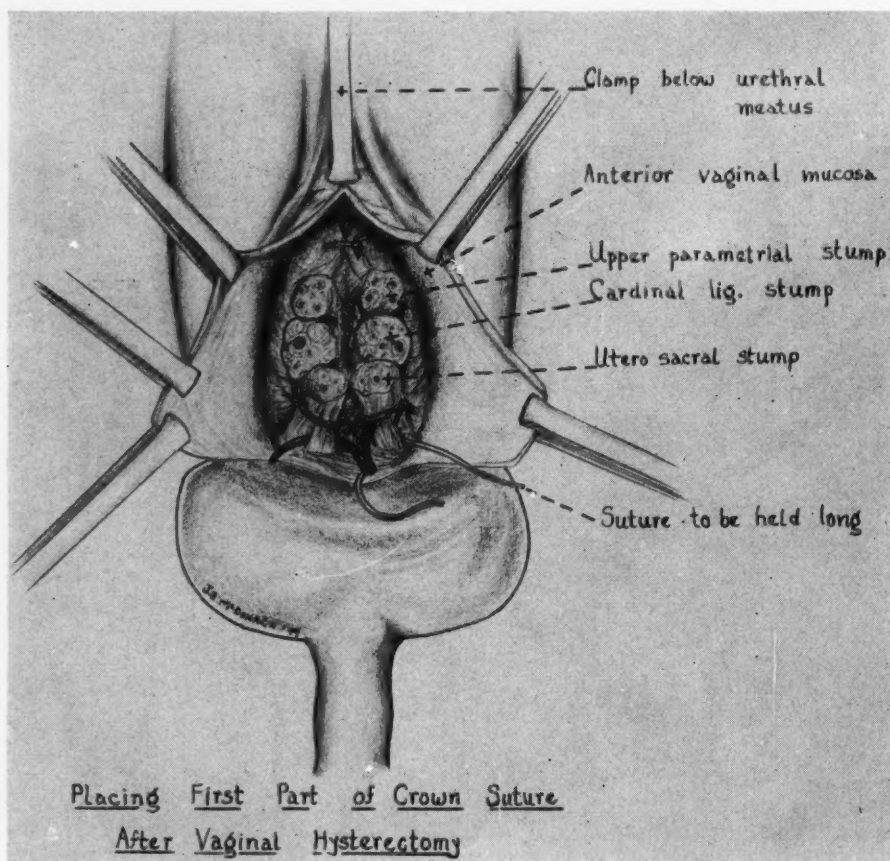


Fig. 6.

The treatment of vault prolapse after hysterectomy, with hernia of Douglas' pouch or high rectocele is different. In many instances no broad ligament structures nor uterosacral ligaments can be found. One must use all other available supporting tissue. The cystocele is corrected by interrupted suture of the musculofascial layers of the anterior vaginal wall after dissection similar to that described for the posterior wall. At the upper extremity of this repair the so-called bladder pillars or lateral stronger portions of the former vesicocervical ligament are caught firmly in a suture of No. 1 chromic catgut which is held long until the posterior vaginal wall has been prepared for repair as in the foregoing

description (Fig. 7). This is used for the crown suture as before, but here in order to anchor the vaginal vault the needle is passed even more laterally to include the stronger medial portion of the connective tissue ground bundle or hypogastric sheath where it is continuous with fascia of the vaginal wall. This necessitates a wider dissection of the vaginal mucosa from its underlying structures at the vault, but these tissues separate easily in the natural lines of cleavage. With vault prolapse the ureters may loop downward to a considerably lower level and in reaching well out for solid supporting tissue, they might be injured. The insertion of ureteral catheters before operation will help to avoid this possible complication. The remainder of the repair is carried out as before.

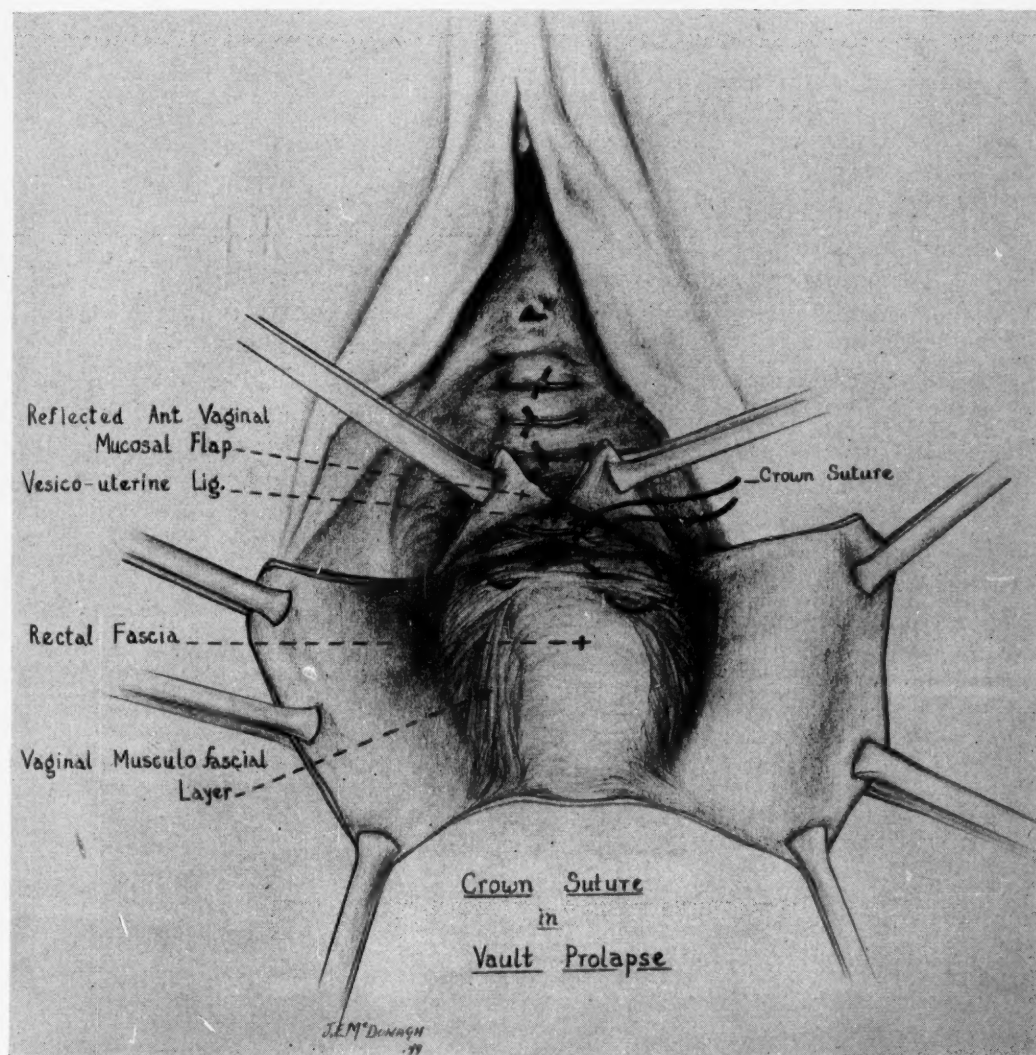


Fig. 7.

### Results

No detailed statistics have been prepared for this presentation, but during the past eleven years these methods of upper posterior vaginal repair have been



employed in all cases where they seemed indicated. This includes practically all cases showing any marked degree of relaxation and includes probably two hundred vaginal hysterectomies, where some repair has been necessary. There have been two cases of so-called recurrence that I know of. Both followed vaginal hysterectomy. Neither of these were recurrences, but were cases where posterior colporrhaphy was not carried to the vault and within one and one-half years the upper posterior wall bulged down over the repaired portion. It was quite evident at the second operation that I had neglected the upper wall, probably because at the time it did not "look too bad." It is far better to do too much than to do too little.

Finally it should be noted that the type of repair herein detailed is simply an attempt to strengthen weakened or torn supportive tissues and to restore them as completely as possible to their normal relationships.

### Summary

1. The etiological differences between hernia of Douglas' pouch and high rectocele have been stressed.
2. Diagnostic methods are discussed.
3. Pertinent anatomical features are reviewed.
4. Techniques of operations based on anatomical reconstruction are suggested for the treatment of these two individual conditions.
5. Variations in operative technique for treatment of hernia of Douglas' pouch and/or high rectocele are detailed: (a) during the course of ordinary vaginal plastic repair procedure; (b) when vaginal hysterectomy accompanies vaginal repair; and (c) in the presence of vault prolapse after previous hysterectomy.
6. Reasons for recurrences and "so-called" recurrences of upper posterior vaginal hernia are given, and the importance of repair of any defect in this region is emphasized.

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## THE REPRODUCTIVE CAREER OF WOMEN WITH OVARIAN DYSFUNCTION\*

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A DEQUATE function of the female genital organs is characterized by normal menstrual cycles which are dependent primarily on the harmonious activity of three interrelated organs; namely, the anterior lobe of the pituitary gland, the ovaries, and the uterus. Menstrual disturbances may be caused by organic and functional defects in any one of these three interdependent organs, the malfunctioning of one being reflected in structural and functional disturbances in one or both of the others. Malfunctions of other endocrine glands may cause disturbances in the menstrual cycle indirectly by virtue of the influence of these glands on the pituitary and the ovaries. We have considered menstrual disturbances caused by intrinsic dysfunction or failure of the ovaries as due to "primary ovarian failure." Such failure is seen in the physiologic menopause and is usually accompanied by a train of clinical symptoms. Secondary ovarian failure follows pituitary dysfunction.

Since the primary purpose of the female genital system is reproduction, it seemed logical to assume that women who had objective evidence of disturbed pituitary and ovarian function, that is, women whose menstrual cycles were disturbed, might have difficulties with the process of reproduction. To test this hypothesis, we studied the reproductive records of 425 young married women who came to the Mayo Clinic because of menstrual disturbances. Of these patients, 58 were from the immediate vicinity and it was possible to follow their condition during their pregnancies.

The menstrual cycles of these patients were generally of two types: The first was characterized by mild disturbances in the rhythm; the intervals varied from two to six weeks and the flow varied from scant to profuse and was with or without associated pain. The second type of cycle which hereafter we shall refer to as a "gross disturbance in rhythm" was characterized by intervals varying from two to six months and in some cases the periods of amenorrhea had lasted as long as a year. Menstrual flow was scant to profuse and was with or without pain. Many of the patients had other symptoms which are commonly seen in women at the physiologic menopause. On the basis of these associated symptoms we divided the patients into two groups: (1) those whose symptoms we considered to be due to primary ovarian dysfunction and (2) those whose symptoms were considered to be due to ovarian failure which was secondary to pituitary dysfunction.

\*Read at the meeting of the American Medical Association, Atlantic City, N. J., June 6 to 10, 1949.

The incidence of obesity and hirsutism was high in our cases. Atrophy of the internal and external genitals and cystic ovaries were usually found on pelvic examination. Many of the women had mastitis.

When the records of reproduction of these 425 women were studied, it was found that 237 (55.8 per cent) of the group had been unable to conceive in an average period of six years (Table I) and 188 (44.2 per cent) had had pregnancies.

TABLE I. SUMMARY OF DATA

Ovarian hypofunction: 425 cases
Sterility: 237 cases (55.8 per cent)
Pregnancies: 188 cases (44.2 per cent)
Only pregnancies which terminated in abortions (Group 1)
54 patients (28.7 per cent)
99 abortions
Ectopic pregnancies with or without other pregnancies (Group 2)
12 patients (6.4 per cent)
13 ectopic pregnancies
2 term pregnancies
6 abortions
"Premature" pregnancies plus abortions in some cases (Group 3)
27 patients (14.4 per cent)
34 premature pregnancies
15 abortions
One term pregnancy plus sterility (Group 4)
47 patients (25.0 per cent)
47 term pregnancies
Term pregnancies, "premature" pregnancies, and abortions (Group 5)
29 patients (15.4 per cent)
34 term pregnancies
6 "premature" pregnancies
39 abortions
More than one term pregnancy plus "premature" pregnancy (Group 6)
19 patients (10.1 per cent)
42 term pregnancies
2 "premature" pregnancies

### Group in Which No Pregnancies Occurred

The average age of the 237 patients who had never been pregnant was 27 years when they were seen at the clinic. They had been unable to conceive in an average period of six years of sterility. Eighty-eight of these women had mild and 149 had gross disturbances in menstrual rhythm. On the basis of associated symptoms, we judged that the ovarian failure of 119 was primary and of 102 secondary. The ovarian failure of the remaining 16 could not be classified from the data at hand.

The most striking physical finding was obesity: 48 patients (20.3 per cent) were obese and of these, 23 whose average age was 30 years, weighed 200 pounds or more (90.7 kilograms). The remaining 25 of the 48 obese patients, whose average age was 25 years, weighed between 165 and 200 pounds (74.8 and 90.7 kilograms). The basal metabolic rate was less than -5 per cent in 15 of the obese patients and was -5 per cent or more in 33.

At attempt to determine the cause of the ovarian dysfunction of some of these 237 women was fruitless because the clinical history had not been taken with this object in mind. Aside from obesity, operations on the ovary, consisting of removal of one ovary or bilateral resection, had produced some degree of hypofunction in many women because of the actual reduction in the amount of functioning tissue and because of the scarring of and the interference with the

blood supply to the remaining tissue. Forty-nine patients (20.7 per cent) of the group had undergone some type of operation on the ovaries. Fifty-five patients (23.2 per cent) had had appendectomies. We suspected that in some of these cases appendectomy had been performed to relieve pain in the right lower quadrant of the abdomen. Frequently the finding of cysts on one or both ovaries leads to resection, so that some of these 55 patients had probably had ovarian surgery also although this is not known definitely.

A review of the family histories of women with ovarian failure many times revealed a high incidence of menstrual and reproductive difficulties in the patient's female siblings and progenitors. Such data led us to suspect that the condition may represent a familial inadequacy.

Infertility of the male partner was a factor in producing the sterility in some of our patients. The husbands of many of these patients were not studied because they did not accompany the patients. Furthermore, the primary object of other patients in seeking medical care was not treatment of the sterility, but relief from the menstrual disorder or the accompanying symptoms or both. We would estimate, however, that sterility of the male was a contributory factor in 30 per cent of these cases.

#### Groups in Which Pregnancy Occurred

The reproductive history of the 188 patients who had conceived was studied. Six types of reproductive history were found and accordingly the patients will be considered in six subgroups as follows: Group 1 consists of patients whose pregnancies had all terminated in abortions; Group 2, of patients who had had one or more ectopic pregnancies, with or without additional pregnancies; Group 3 of patients who had had only pregnancies which had terminated in premature labor, called hereafter in this paper "premature" pregnancies (some of these also had had abortions); Group 4, of patients whose only pregnancy was one full-term pregnancy. Group 5 consists of patients who had had one or more full-term pregnancies and one or more pregnancies that had terminated in abortions with or without premature pregnancies. In Group 6 were patients who had had more than one full-term pregnancy and no pregnancies which had terminated in abortions. The number of patients in each group and the type of pregnancies are listed in Table I. The conditions obtaining in the six groups are included in Tables II, III and IV. In Table II is given the number of cases in each group of mild and gross menstrual irregularities, primary and secondary ovarian failure, and the basal metabolic rates of less than -5 per cent. In Table III is given the incidence of the various complications of pregnancy in each group and in Table IV the data concerning infants.

We shall discuss briefly some of the conditions obtaining in each group.

*Group 1.*—The pregnancies of 54 patients (28.7 per cent of the 188 women) had all terminated in abortions. The last pregnancies of these women had been followed by an average period of 6.25 years of sterility. The type of menstrual disturbances, the type of ovarian failure, and the basal metabolic rates are given in Table II. Of these women, 16.6 per cent were obese, that is, weighed more than 165 pounds (74.8 kilograms). Eleven had had some type of operation on the ovaries and 13 had had appendectomies. The total number of pregnancies was 99, or approximately 2 per patient.

*Group 2.*—Our second group is composed of 12 patients (6.4 per cent) (Table I) all of whom had had ectopic pregnancies. These 12 patients had had 13 ectopic pregnancies, 2 term pregnancies, and 6 that terminated in abortions. Their average age was 31.5 years and the average period of sterility was 8.6 years. Data on the menstrual irregularities, type of ovarian dysfunction, and basal metabolic rates are given in Table II. Two infants were born at term;

one of these was delivered after a prolonged labor of twenty-eight hours and survived; the other succumbed fourteen hours post partum of birth injuries. Hence, of twenty-one pregnancies, only one had a successful outcome. Four of the patients lost an ovary at the time of salpingectomy.

TABLE II. RELATIONSHIP OF TYPE OF OVARIAN FAILURES AND PREGNANCY

	GROUPS						TOTAL
	1	2	3	4	5	6	
Number of patients	54	12	27	47	29	19	188
Average age, years	28.2	31.5	24	25.9	30.4	28.7	28.1
Years of sterility, average	6.25	8.6	4.2	4.8	7.5	5.5	6.14
Menstrual irregularities:							
Mild	29	5	13	16	23	15	101
Gross	25	7	14	31	6	4	87
Ovarian failure:							
Primary	28	9	14	27	21	12	111
Secondary	10	1	8	13	2	2	36
Indeterminate	16	2	5	7	6	5	41
Basal metabolic rate of -5 per cent or more*	26	1	12	27	18	6	90*
Basal metabolic rate of less than -5 per cent*	16	9	13	19	9	9	75*
Abortions	99	6	15	0	39	0	159
"Premature" pregnancy		0	34	0	6	2	42
Term pregnancies		2	0	47	34	42	125
Ectopic pregnancies	0	13	0	0	0	0	13
Number of living children after neonatal period		1	8	42	35	40	126

\*The basal metabolic rates of all patients were not determined.

TABLE III. COMPLICATIONS OF PREGNANCY

	GROUP					TOTAL
	2	3	4	5	6	
Number of patients	12	27	47	29	19	134
Eclampsia	0	1	1	2	0	4
Pre-eclampsia						
Severe	0	7	8	2	2	19
Mild	0	0	3	5	6	14
Abruptio placenta	0	2	0	1	0	3
Placenta previa	0	0	0	1	0	1
Prolonged labor (labor of more than twenty hours)	1	2	8	7	9	27
Postpartum hemorrhage	0	2*	1	3	1	7
Cesarean section	0	1	4	1	0	6

\*Hysterectomy necessary in one.

**Group 3.**—In this group were 27 patients of an average age of 24 years and with an average period of sterility of 4.2 years. These 27 patients had had only pregnancies that ended in premature labor (designated herein as "premature" pregnancies) with or without abortions (Table II). The type of menstrual irregularities, the basal metabolic rate, and the type of ovarian failure are given in Table II. Only 2 patients were obese. One patient had had an oophorectomy; 2 had had ruptured appendices, and 5 more had had appendectomies. This makes 7 who had undergone appendectomies.



The course of early pregnancy was complicated by nausea and vomiting, pelvic pain, and bleeding in approximately half of this group. During the third trimester, 1 patient had eclampsia, 7 severe pre-eclampsia, 2 had premature separation of the placenta and 2 prolonged labors. Two patients had postpartum hemorrhages, 1 of which required hysterectomy for control of bleeding. There was one cesarean section for severe pre-eclampsia (Table III).

The total number of pregnancies in this group was 49, of which 15 were abortions. Of the 36 premature infants (2 sets of twins), only 8 survived. Two of the 36 infants had congenital defects incompatible with life. The total number of infants with congenital defects was 3 (Table IV).

TABLE IV. DATA CONCERNING INFANTS

	GROUP					TOTAL
	2	3	4	5	6	
Number of mothers	12	27	47	29	19	134
Infants living at term	2*	0	44†	34‡	40‡	120 (113 lived)
Premature						
Lived	0	8	0	3	2	13
Died	0	28	0	3	0	31
Stillborn	0	1	3	2	2	8
Congenital anomalies	0	3§	4	4	4	15
Large babies (more than 3,500 grams)	0	0	3	11	11	25

\*One died fourteen hours after birth.

†One died first day of life of congenital deformity and one died first day of life of birth trauma.

‡Two died in neonatal period.

§One stillborn infant.

*Group 4.*—This group is composed of 47 women of an average age of 25.9 years. Each had one term pregnancy which had been followed by an average period of 4.8 years of sterility. Thirteen of the group were obese. Five had had ovarian surgery and 14 had had appendectomies.

The pregnancies were accompanied by a high incidence of complications. Details were lacking for 15 patients, but in the remaining 32, the pregnancy was attended by some kind of trouble. The prenatal period was accompanied by nausea and vomiting, bleeding, headaches, and pelvic pain in 8 of the group. In the third trimester, 1 patient had eclampsia, 8 had severe pre-eclampsia and 3, mild pre-eclampsia. One fourth of the 32 patients had labors that lasted longer than twenty hours. Of the 4 cesarean sections done, 3 were for toxemia and 1 for a contracted pelvis. Forty-four living infants were born at term; 1 of these died on the first neonatal day of life of congenital defects and a second died on the first neonatal day of birth trauma. Three infants were stillborn. Four of the group had some type of congenital defect (Table IV).

*Group 5.*—The 29 women in this group were an average age of 30.4 years and had had an average period of sterility of 7.5 years. Each had had term pregnancies and abortions with or without "premature" pregnancies. Three of this group were obese. Four had had some type of ovarian surgery and an additional 9 had had appendectomies.

Pregnancy was again attended by complications. Three of the patients had no difficulties, 1 of whom had had treatment. We had no details as to the course of the pregnancies of 5 of the patients. Eleven of the group had had pelvic pain, nausea, vomiting, and headache; 6 others bled some time during the prenatal period. Two patients had eclampsia, 2 severe pre-eclampsia, and 5 mild pre-

eclampsia; 1 patient had a partial premature placental separation. Seven of the group had prolonged labors; 3 had postpartum hemorrhages severe enough to require transfusion.

This group of women had had a total of 34 term and 6 "premature" pregnancies and 39 abortions. Four infants had congenital defects (Table IV). One monster and 1 hydrocephalic infant born at term succumbed in the first few hours of life. Two other term infants had congenital defects not incompatible with life. Eleven of the term infants weighed more than 3,500 grams. Three of the 6 premature infants and 32 of the term infants survived, hence, of a total of 79 pregnancies, this group of women had 35 living children.

*Group 6.*—The average age of the 19 women in this group was 28.7 years and the average period of sterility was 5.5 years. Each woman had had more than one term pregnancy. Only one of these women was obese. Two of these women had had operations on the ovary and 5 had had appendectomies.

The incidence of complications of pregnancy was least in this group. Two patients had severe pre-eclampsia, and 6 had mild pre-eclampsia (Table III); 9 had prolonged labors and 1 had a postpartum hemorrhage.

This group of women had 42 term and 2 "premature" pregnancies. Two of the term infants were stillborn and 2 had congenital defects; 1, a monster, died shortly after birth and the second succumbed on the fourth neonatal day of congenital heart disease. Two additional infants had congenital defects not incompatible with life. Hence, of a total of 44 pregnancies, 40 ended successfully. While the number of patients in this group is too small to be significant statistically, the trend of the data suggests that when the ovarian failure is mild, the complications of pregnancy are fewer than in the other group and the successful outcome of the pregnancies is higher.

#### Summary of Data on 425 Patients

Of the 425 patients with menstrual irregularities studied, 237 (55.8 per cent) had never conceived and 188 (44.2 per cent) had been pregnant.

Eighty-eight of the sterility group and 101 of the group who had had conceptions had mild disturbances in menstrual rhythms while 149 of the sterility and 87 of the group with conceptions had gross disturbances in the menstrual rhythms. Forty-eight of the women who were sterile and 28 of those who had had conceptions were obese; that is, approximately 17.9 per cent of the entire group of 425 patients were obese. Some type of ovarian surgery had been performed on 20.7 per cent of the women who were sterile and 14.4 per cent of the others; that is, 17.9 per cent of the entire group. Appendectomies had been performed on 23.2 per cent of women who were sterile and 25.5 per cent of the others; that is, on 24.4 per cent of the entire group. The 188 women who had had conceptions had had a total of 339 pregnancies, of which 159 had ended in abortions; there were 13 ectopic pregnancies, 42 "premature" pregnancies, and 125 term pregnancies. From these 339 pregnancies there were 126 living children, less than 1 per patient. Twenty-five (19.8 per cent) of these infants weighed more than 3,500 grams; 15 infants had congenital anomalies, an incidence of 8.9 per cent of the term and premature infants in contrast to an expected incidence of 1.8 per cent. The incidence of complications of pregnancy was much greater than average. There were 4 cases of eclampsia, an incidence of 2.4 per cent of the term and "premature" pregnancies as compared with a usual incidence of 0.3 per cent, and 19 cases of severe pre-eclampsia, an incidence of 11.4 per cent, and 14 cases of mild pre-eclampsia, an incidence of 8.4 per cent. The total number of cases of pre-eclampsia was 33 (19.8 per cent) as compared with the usual incidence at the clinic of 3 per cent. Prolonged labor complicated 26 of the term and 1 "premature" pregnancy (16.2 per cent). Postpartum hemorrhage occurred in 7 patients, an incidence of 4.2 per cent.

It is evident from this study that this group of women with menstrual irregularities had a high incidence of sterility. When they conceived they had abortions, ectopic pregnancies, and premature termination of their pregnancies. Pregnancy was accompanied by a high incidence of toxemia, prolonged labor, stillbirths, and malformed infants. The total fetal survival was low.

### Comment

Over a period of two decades, Young<sup>1</sup> has called attention to what he called the "abortion toxemia taint." He has shown that patients who have had antecedent pregnancies ending in abortion, premature birth, or stillbirth have a high incidence of toxemia in the pregnancy immediately following. He reported that only 54.2 per cent of a group of 142 pregnancies, following previous pregnancies that had ended in abortion, premature birth, or stillbirth, were normal and toxemia complicated 17.6 per cent of the 142. Thus the "abortion toxemia taint" is frequently recurrent in the sense that it is apt to reappear in successive pregnancies. He has concluded that there is a constitutional background to the abortion toxemia taint that is hormonal.

Other significant clinical papers suggesting that there is some relationship between the patient's ovarian function and the complications of pregnancy have appeared during the last several decades. Vorzimer, Fishberg, Langrock and Rappaport<sup>2</sup> from a study of 120 toxemic patients have given evidence "that toxemia is an endocrine disturbance evolving in women with a pre-existing constitutional abnormality of the endocrine glands." They were concerned in their study with the physical and laboratory findings. We surmise from their report that a review of their patients' menstrual histories might have revealed abnormalities.

White's<sup>3</sup> study of girls with diabetes has shown that many of these individuals exhibit signs of hypo-ovarianism as suggested by the frequency of amenorrhea, metrorrhagia, and retardation of growth. She has observed in these patients a hormonal imbalance characterized by normal or high titers of follicle-stimulating hormone and low excretion of 17-ketosteroids. These observations are suggestive of normal pituitary function with gonadal or adrenal failure. When these girls become pregnant, with their hypo-ovarianism and vascular disease, their obstetrical course includes many abnormalities. Miscarriage, premature labor, toxemia, and uterine inertia are frequent in occurrence. Fetal wastage has been high. The incidence of congenital anomalies among the infants born to these patients was 12 per cent as compared with an expected incidence of 1.8 per cent. The birth weight of 80 per cent of the infants exceeded the normal, and the body length of the same percentage exceeded the average for the chronologic age. White said in conclusion that the abnormal course of the obstetrical patient who has diabetes may be sought in the maternal background, the abnormalities of which are vascular, chemical, endocrine, and genetic.

Another cause of diminishing ovarian function is that of aging, which in itself adds an additional handicap of a certain amount of vascular impairment. Davis and Seski<sup>4</sup> recently studied a group of 1,011 women who went through pregnancy after they were 40 years of age. Of these, 16.8 per cent were primiparas 83.2 per cent were multiparas who had an interval of at least ten years since the last previous pregnancy. No data were given on the patient's menstrual histories or previous reproductive experience. These women had a significantly higher incidence of complications of pregnancy than obstetrical patients as a whole. Toxemia of pregnancy developed in 1 of every 4 patients. The incidence of placenta previa and abruptio placentae were materially increased, as were breech and transverse presentations. The incidence of postpartum hemorrhage also was high.



The infants also suffered from the increased hazards of childbearing; 1 of every 10 mothers failed to take a baby home with her. The high fetal mortality rate was a result of increased numbers of premature babies, an increased number of congenital anomalies, and a high incidence of fetal damage because of the greatly increased number of complications of pregnancy.

Whether certain cases of obesity are secondary to genital hypofunction or whether the hypofunction results from the obesity is debatable. In either case, the obese woman who becomes pregnant has some degree of ovarian hypofunction. That the obstetrical career of these obese women is complicated has been shown by Matthews and Der Brucke's<sup>5</sup> study. Of their group of 200 women weighing more than 200 pounds (90.7 kilograms), 75 per cent had some type of complication of pregnancy. Toxemia accounted for the largest number of complications as 89 women (44.5 per cent) were affected. Five patients (2.5 per cent of the group) had eclampsia; 10 had severe pre-eclampsia. Abnormal presentations occurred in 26 per cent. Because of these malpresentations and positions, labor was prolonged. To this, they stated, uterine inertia was frequently contributory. Operative delivery was increased and, with its frequent complication, postpartum hemorrhage, rose to 7 per cent. Of the 202 infants born, 25 (12.3 per cent) died; 8 ante partum, 11 intra partum and 6 post partum. At birth 57.5 per cent of the infants weighed more than 3,600 grams.

Benda,<sup>6,7</sup> from his study of mongolism, has shown that this congenital disorder is related to the maternal condition at the time of the pregnancy. He pointed out as have others, that such infants occur either at the beginning of the reproductive career or at the end. These times he called "the threshold of sterility." At the beginning of a reproductive career the maternal organism is physiologically immature and later the maternal organism is old. He also has noted a high incidence of thyroid disturbance, history of previous abortions, premature labors, relative infertility, and bleeding in pregnancy.

Review of the data from the literature and our data suggests that from prospective mothers it is possible to pick those women who have a greater than normal chance of having difficulties with the reproductive process and that treatment for these then may be started before conception. Therapy to improve ovarian function by general measures, as hygienic living, and diet, improvement of the menstrual rhythm by use of estrogen, thyroid, stimulating roentgen therapy to the pituitary and ovaries will insure a better "seedbed" for the pregnancy. Perhaps reduction of the number of pelvic operations for lower abdominal or pelvic pain also would help to improve the gloomy outlook for many of these women.

Since the group of women with ovarian failure contributes a proportion of the patients with toxemia, premature labor, uterine inertia, prolonged labor, unsuccessful outcome of pregnancy with stillbirth and congenital anomalies, we believe treatment of this group of women before pregnancy should be one positive means of reducing these complications of pregnancy.

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## THE SYNDROME OF LOWER NEPHRON NEPHROSIS FOLLOWING HEMORRHAGIC SHOCK

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**D**URING recent years, considerable clinical and experimental data have accumulated concerning a distinctive kidney lesion which follows severe and prolonged shock. Having as yet no generally accepted name, it has been called "hemoglobinuric nephrosis,"<sup>1</sup> "lower nephron nephrosis,"<sup>2</sup> "shock kidney,"<sup>3</sup> and "kidney lesions of the crush syndrome."<sup>4</sup> All of these terms refer to degeneration and necrosis of the tubules below the loop of Henle associated with the presence of heme casts. The lesion, in most instances, is apparently due to renal anoxia, and the degree of severity is directly dependent on the extent and duration of the anoxia.

The clinical picture of this condition consists of a symptom-complex which is usually initiated by a period of severe and prolonged shock. Treatment by infusions is followed by recovery from the shock with a normal blood pressure and pulse rate. The initial oliguria, however, persists with an increasing azotemia, mental lethargy, and hypertension. This proceeds to edema, uremia, coma, and death. The length of the entire course is approximately a week to ten days.

This syndrome should be of great interest both to obstetricians and gynecologists because of the many emergencies associated with shock. An understanding of these remote changes following recovery from shock is essential for the diagnosis, prognosis, and proper management of the condition.

A case illustrating this syndrome, with eventual recovery and a three and a half year follow-up, is herewith presented. This patient was treated on the Obstetrical Service of Bellevue Hospital, and special renal clearance studies were performed by the Department of Physiology of New York University School of Medicine.

### Case Report

Mrs. G. G., a 22-year-old Negro woman, gravida ii, para i, at term, was admitted Aug. 13, 1945, at 10:00 P.M., in early labor.

*Past History.*—A previous pregnancy in 1943 terminated in a forceps delivery of a 6 pound, 14½ ounce male infant after a twenty-four hour labor at another hospital. There were no postpartum complications. Medical and surgical history was negative.

During the present pregnancy, serological evidence of syphilis was discovered in the Prenatal Clinic. The patient was treated with penicillin at Bellevue Hospital for ten days in March, 1945.

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*Intrapartum Course.*—On admission, labor pains were very mild. General physical examination was negative. Abdominal examination revealed an estimated 7 pound fetus in left occipitoanterior position with a floating vertex and a good fetal heartbeat.

On admission, blood pressure was 130/80, urinalysis was negative, red blood cells, 4.3 million, hemoglobin 11.5 grams. Wassermann and Kahn tests were negative.

At 1:45 A.M., labor became more active with pains occurring every two minutes. At 4:50 A.M., vaginal examination revealed the cervix to be soft, four fingers dilated, with the head at the spines in right occipitoposterior. The fetal heart rate, between contractions, was 70 and grossly irregular. Although the cervix became fully dilated, no progress was made despite good bearing-down efforts and attempts to rotate the head manually. In view of the fetal distress and the lack of progress, it was decided to terminate labor with forceps. The patient was anesthetized with ether, and the fetal heart beat became regular and rose to 110. Kielland forceps were applied and the head was pushed up above the spines and rotated anteriorly. At 6:40 A.M., an apparently normal male child, weighing 6 pounds, 12½ ounces, and measuring 19 inches in length, was delivered. The cord was wound about the baby's right shoulder and right leg. The baby breathed and cried after aspiration and oxygen inhalation. After a third stage of five minutes, the placenta and membranes were expressed intact, and the episiotomy was repaired.

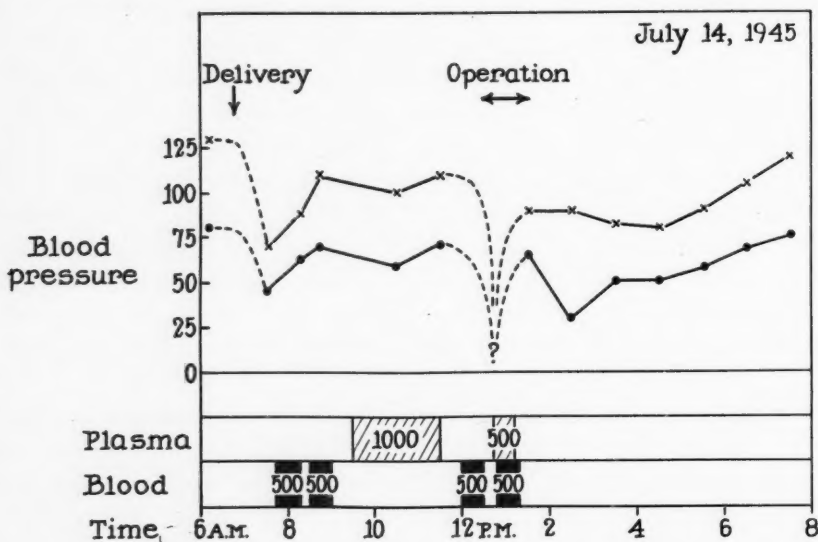


Fig. 1.—Course of blood pressure during shock period. Blood and plasma therapy is indicated.

Vaginal bleeding continued and the blood pressure fell to 70/40. The cervix was inspected and bilateral lacerations were repaired, during which the patient received 500 c.c. of cross-matched blood. An estimate of the total blood loss at this time was 600 c.c. The fundus remained firm and well contracted.

The blood pressure responded slowly to the transfusion, rising to 88/64 with a pulse of 88, of good quality. At 8:30 A.M., a second transfusion of 500 c.c. of blood was started. The blood pressure rose to 110/70 and the patient was kept well sedated with morphine. At 9:00 A.M., a soft, suprapubic mass was noticed at the bladder site and the fundus was pushed to the right just below the umbilicus. The patient was given 500 c.c. of blood plasma at 9:30 A.M., followed by a second 500 c.c. at 10:30 A.M. The blood pressure remained in the vicinity of 100-110/60-70. At 10:30 A.M., it was noticed that the soft suprapubic mass previously described was larger and that the uterus was two fingers above the umbilicus and pushed to the left. Catheterization of the bladder showed little urine return. A diagnosis of rupture of the lower uterine segment was made.

The patient was brought to the operating room at 12:30 P.M., with a 500 c.c. blood transfusion running in the left arm. Shortly after the start of the operation, the blood pressure was unobtainable, but a very faint carotid pulse could be detected. A cut-down was performed at the right ankle and 500 c.c. of plasma started. Under minimal gas, oxygen, and ether anesthesia, the peritoneal cavity was entered. The uterus was soft, boggy, two fingers above the umbilicus and pointing toward the left. A small amount of free blood clot was found near the left iliac fossa. Near the left uterosacral ligament there was a complete uterine perforation, 1 cm. in diameter, from which blood was oozing. The lower uterine segment was tremendously dilated and markedly edematous. Upon incising the visceral peritoneum at the point of external rupture, a large incomplete rupture of the lower

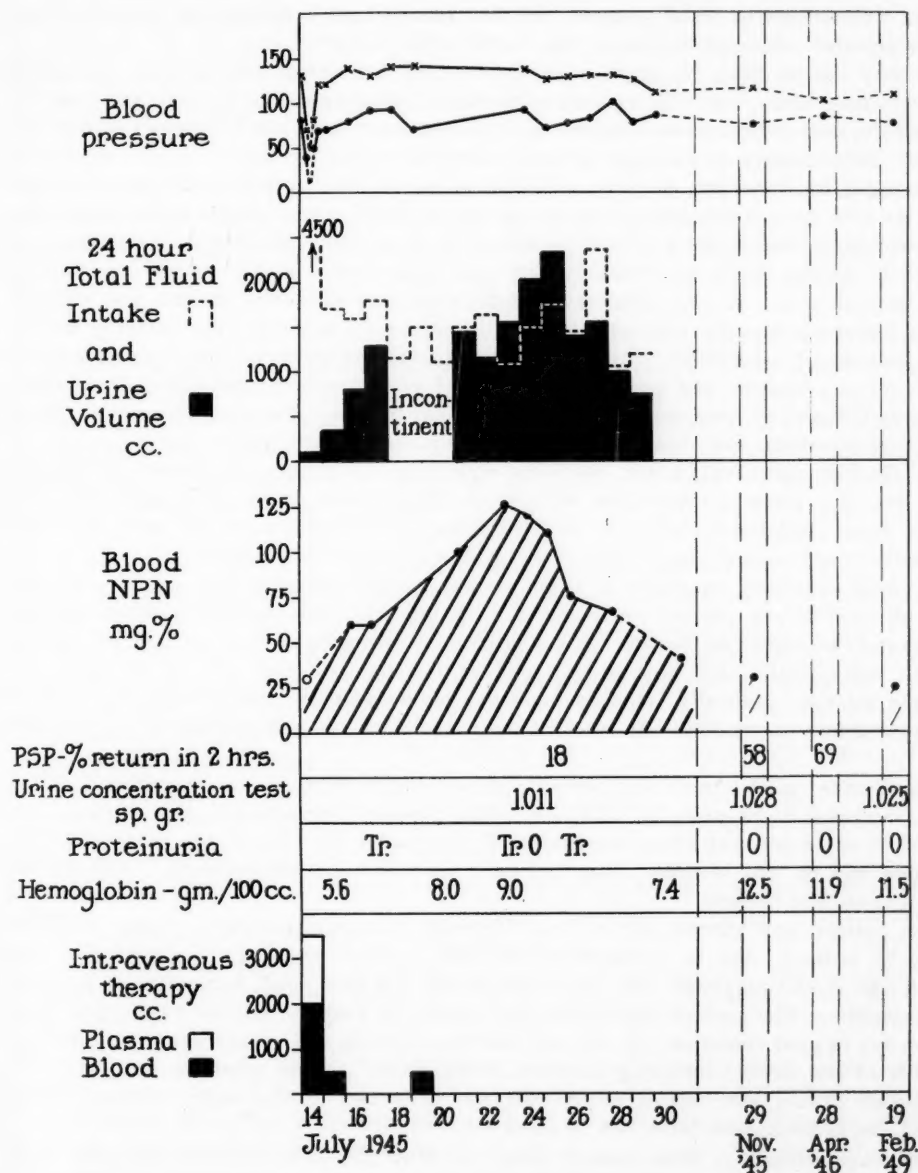


Fig. 2.—Summary of pertinent clinical and laboratory data. Note the fallacy of using the nonprotein nitrogen as a prognostic guide. Although it is rising, the urine output is increasing at the same time, showing return of kidney function.

uterine segment was found, 5 cm. in diameter. Over 500 c.c. of clotted blood were removed from the lower uterine segment through this large perforation. A supracervical hysterectomy was then performed. The uterine arteries were collapsed and white in color and no pulsations were noted. Five grams of sulfanilamide were left in the peritoneal cavity. Blood pressure following the operation was 90/65. At this time the estimated blood loss was 1,500 c.c. but was probably much greater, and the patient had received 2,000 c.c. of whole blood and 1,500 c.c. of plasma. She was returned to the ward in fair condition.

*Postoperative Course.*—For the first six hours following operation, hourly blood pressures were reported as follows: 90/65, 90/30, 82/50, 80/52, 90/64, and 105/68. Radial pulse rates varied in the vicinity of 150. Subsequent to this, the blood pressure rose to 120/75, then to 140/90 for the next few days and thereafter remained within normal limits.

The fluctuations in blood pressure and the therapy given during her immediate pre- and postoperative stages are shown in Fig. 1.

Urinary output (Fig. 2) was 10 c.c. in the first six hours, and 100 c.c. during the first twenty-four hours. Succeeding twenty-four-hour periods yielded 350, 800, and 1,300 c.c. Following this, the patient became incontinent of urine and feces, but the output seemed satisfactory. Subsequently, a moderate diuresis occurred.

During a lucid moment the day following operation, the patient complained of blindness in the left eye. A diagnosis of occlusion of the left central retinal artery was made.

Temperature rose to 101.4° F. on the second postoperative day, dropped to normal, rose to 100.4° F. on the fourth postoperative day, and thereafter remained normal for the rest of her hospital stay. For the first seven days after operation, the patient was mentally confused, spoke incoherently, and complained of vertigo and headache. The lower lip became swollen because of involuntary biting. On the eighth postoperative day, coincident with the onset of the diuresis and reversal of the blood nonprotein nitrogen trend, she cleared mentally and disclaimed any memory for postoperative events. The operative wound healed well by first intention, and clips were removed on the sixth postoperative day.

On the first postoperative day, red blood cells were 2.8 million and hemoglobin was 5.6 grams. She was given a transfusion of 500 c.c. whole blood on the first and fifth postoperative days. Red blood count rose to 3.0 million and 3.5 million on the sixth and ninth postoperative days with a hemoglobin of 8.0 and 9.0 grams, respectively.

A blood chemistry examination taken on her second postoperative day showed nonprotein nitrogen 60 mg. per cent, uric acid 5.3 mg. per cent. On succeeding determinations, the nonprotein nitrogen rose to 100 mg. per cent on the seventh, and to 129 mg. per cent on the ninth postoperative day, with a uric acid of 6.7 mg. per cent. From this peak, the nonprotein nitrogen gradually fell to normal on the seventeenth postoperative day. Intravenous pyelograms on the fifth day revealed the presence of contrast medium in both urinary tracts.

Renal tests on the tenth day showed marked impairment of concentrating function, with an increased night urine of 1,125 c.c. The phenolsulfonephthalein test showed a dye return of 15 to 18 per cent after two hours. Urinalysis on the eleventh day showed a trace of albumin and on two occasion many pus cells were found microscopically. This cleared quickly without any therapy.

The patient was allowed up on her nineteenth postoperative day. There was some difficulty in walking, due to weakness of the left leg. A neurological consultation was obtained, and it was suggested that the weakness was due to a small infarction of the right internal capsule. The patient was discharged from the hospital on the twenty-first postoperative day in good condition. It was felt that the azotemia and renal damage were entirely the results of the severity and long duration of the shock. It was similarly considered that the occlusion of the left retinal artery and the infarction in the right internal capsule were both due to thrombosis secondary to shock.

She was re-admitted three months later, on Nov. 29, 1945. There was only slight difficulty in walking. Phenolsulfonphthalein test showed a 58 per cent return in two hours. Concentration and dilution tests showed a normal night urine of 270 c.c. and a high specific gravity of 1.028; after hydration, this became lowered to 1.008.



The patient was again seen in April, 1946. Concentration and dilution tests were normal. Phenolsulfonphthalein return was 68.9 per cent. Vision of the left eye was absent except for light awareness.

In February, 1949, a urea clearance showed 64 per cent of average normal. The concentrating function was still normal.

*Special kidney studies.*—The glomerular filtration rate, effective renal plasma and blood flow, and tubular excretory mass were estimated from the renal plasma clearances of mannitol and p-aminohippurate, using the techniques outlined by Goldring and Chasis.<sup>5</sup> The first of these studies was made on the sixteenth postshock day, at which time the blood nonprotein nitrogen had just fallen to the upper limit of normal. As shown in Table I, the results were all well below the normal range at this time. By the thirty-ninth day, glomerular filtration and effective renal plasma flow had risen to just below the normal range. In fact, there was no significant change in these two measurements twenty weeks and forty-one weeks after the shock episode. However, the tubular excretory mass, which in this case was measured as the maximum rate at which the tubules excreted p-aminohippurate ( $Tm_{PAH}$ ), had not reached its maximum value at thirty-nine days. Thus, there is an apparent difference in the rate of recovery of this tubular function as compared to the glomerular filtration and renal blood flow. The  $Tm_{PAH}$  achieved its maximum recovery sometime between the thirty-ninth day and twentieth week after shock.

Whether the recovery values shown are below the patient's preshock levels is not known, since control measurements were not made. On statistical grounds, it is possible for her functions to have been slightly below the range indicated in the table, and still be considered normal. However, it is also possible that the preshock values had been higher and that, therefore, some permanent destruction of renal tissue may have occurred. A choice between these two alternatives cannot be made from the available data.

TABLE I. SUMMARY OF RENAL CLEARANCE STUDIES

DATE	POST-SHOCK INTERVAL	SURFACE AREA (SQ. M.)	HEMATO-CRIT PER CENT	GLOMER-ULAR FILTRATION RATE* (C.C. PER MINUTE)	EFFECTIVE RENAL PLASMA FLOW* (C.C. PER MINUTE)	EFFECTIVE RENAL BLOOD FLOW* (C.C. PER MINUTE)	UREA CLEAR-ANCE (PER CENT OF AVER-AGE NORMAL)	TUBULAR EXCRETORY MASS ( $Tm_{PAH}$ )* (MG. PER MINUTE)
7/30/45	16 days	1.43	22	46	258	332	-	33
8/22/45	39 days	1.37	-	76	356	-	-	49
11/30/45	20 weeks	1.36	37	68	362	576	-	67
4/29/46	41 weeks	1.38	35	83	387	592	-	64
2/19/49	3½ years	1.37	34	-	-	-	64	-
Normal Average		-	-	117	594	982		77.5
Range†				86-148	389-799	613-1351		51.7-103.3

\*Corrected to body surface area of 1.73 square meters.

†The values for glomerular filtration rate, plasma flow, and blood flow are from the series of normal women summarized by Smith<sup>18</sup>, and those for  $Tm_{PAH}$  are from the combined series of normal men and women studied by Chasis, Redish, Goldring, Ranges, and Smith.<sup>19</sup>

In the follow-up renal study three and a half years post shock, the urea clearance was found to be 64 per cent of average normal. This corresponds closely to the filtration rate and plasma flow in the previous three studies, since they also averaged about 65 per cent of average normal. It can be concluded, therefore, that there was no progressive renal disease resulting from the shock, and that maximum recovery occurred sometime between the thirty-ninth day and twentieth week.

### Comment

*Experimental Data.*—The effects of shock on the kidney may be divided into two phases:<sup>3</sup>

In the first or ischemic phase, the effects are circulatory. A blood pressure drop below 70 mm. Hg usually causes urine formation to cease and azotemia to begin, by reducing the hydrostatic pressure in the glomerular capillaries to a point where it can no longer overcome the osmotic pressure of the plasma colloids.<sup>6</sup> The effective plasma flow and the rate of glomerular filtration are reduced approximately in proportion to the degree of shock.<sup>7</sup> This decrease is greater than can be accounted for on the basis of reduced arterial pressure alone, thus suggesting an active vasoconstriction in the renal arterioles. Such renal shutdown appears to be a homeostatic reaction to the loss of circulating blood volume, and is useful in sustaining the more vital organs, such as the brain.<sup>3</sup> The renal circulation may at first be only partially restored by full blood replacement. Although the filtration rate increases, the renal blood flow tends to remain low with only a gradual return to normal levels.

In the second or renal damage phase, the kidneys fail to resume normal function even though the general circulation has been adequately restored. Anuria or oliguria continues and azotemia increases. Depending on the amount of kidney damage, this period may be short, lasting only a day or two, or it may continue into fatal uremia.

This second phase has been simulated experimentally in dogs by Van Slyke and associates.<sup>8, 9</sup> After unilateral nephrectomy, two serrefines were applied to the renal artery. If the clamps were removed after two or three hours, the original renal blood flow was only partially restored, and a rise of blood urea to over 150 mg. per cent occurred during the next four days. Subsequent to this, the blood urea gradually fell to normal in two or three weeks, and the urea clearance returned to the control level. If the clamps were allowed to remain for four hours, only 50 per cent of the dogs survived. A mortality of 100 per cent from uremia occurred if the clamps remained for six hours. Pathological examination of the kidneys of dogs dying of uremia showed tubular changes resembling those seen in the crush syndrome. The glomeruli showed little change other than a slight thickening. Badenoch and Darmady<sup>10</sup> partially occluded the renal artery in rabbits with similar results.

It appears, then, that renal ischemia brought about by local vasoconstriction due to shock can lead to uremia if the shock is sufficiently severe and prolonged. One of the reasons for the susceptibility of the kidney to anoxia may be due to the fact that unlike other organs the oxygen consumption of the kidney diminishes in proportion to the decrease in renal blood flow.<sup>11</sup> Other tissues can tolerate a decrease in perfusing blood volume by extracting increased amounts of oxygen, but despite marked decreases in the renal blood flow little additional oxygen is extracted by the kidney.

The case reported here is roughly equivalent to the dogs whose renal arteries were clamped for two hours. Sufficient renal damage occurred to produce azotemia and hyposthenuria, but this damage was temporary and reversible.

Similar clearance studies showing the reversibility of this type of kidney damage have been described by Burnett and associates<sup>20</sup> and by Marshall and Hoffman.<sup>21</sup>

*Prognosis.*—Lucké<sup>2</sup> feels that hypertension is a cardinal sign of the syndrome and occurs early on the third day. Mallory<sup>1</sup> finds it to be inconstant but of grave import when present. In our reported case, a slight but transient hypertension occurred, and this suggests that the absence of hypertension or a transient one is a good prognostic sign.

Another important sign is the urinary output. If this is on the increase after forty-eight to seventy-two hours, a favorable outcome is to be expected despite a rising nonprotein nitrogen. Persistence of the oliguria points to extreme renal damage. The work of Van Slyke and associates, referred to above,<sup>8, 9</sup> emphasizes the prognostic value of repeated urea clearance measurements. If the urea clearance rises, kidney function is returning even though the azotemia is increasing. Utilizing this test, it should be possible to predict the outcome with reasonable accuracy early in the course of the disease.

*Treatment.*—In view of the foregoing, the duration of time a patient is allowed to remain in shock becomes of paramount importance. Prompt replacement of blood volume is essential if severe and even fatal kidney damage is to be avoided. Wiggers<sup>12</sup> believes that infusions of sodium bicarbonate should also be given as it may help to prevent the development of irreversible shock and combats the associated acidosis.

Once the condition has developed, a high-calorie, low-protein diet which minimizes the formation of nitrogenous products has been suggested.<sup>13</sup> Fluid intake should be carefully regulated and should not be over 2,000 c.c. if oliguria is present. It is important not to overhydrate these patients because of the danger of pulmonary edema and cardiac failure. The oliguria will not respond to overhydration but is dependent entirely on the return of tubular function. Measurement of the plasma carbon dioxide provides the basis for combating acidosis. Sodium bicarbonate or lactate should be administered, orally if possible, otherwise intravenously, but the amounts given should be governed not only by plasma carbon dioxide but also by consideration of their effect on fluid retention. A careful record of urinary output and fluid intake, daily blood pressure, and urinalysis which includes the benzidine test should be kept. Blood nonprotein nitrogen, or preferably the urea clearance, should be measured repeatedly. If anemia is present, small transfusions and iron therapy can be given.

Splanchnic nerve block has been used in an attempt to counteract the local renal vasospasm.<sup>14, 15</sup> This procedure appears to be rational if performed early, but in at least one case<sup>15</sup> showed little clinical result. Further study is necessary to determine its proper place in the therapy of this condition.

Peritoneal irrigation has been found to be valuable in this condition,<sup>16, 17</sup> and appears to be indicated in the presence of a persistent oliguria. The operative technique is simple, but the danger of infection has not been completely eliminated.<sup>17</sup> The use of the artificial kidney is not as yet available generally. Both of these procedures are calculated to eliminate nitrogenous waste products and restore electrolytic equilibrium until the kidney has recovered sufficiently to carry on these functions.

### Summary

A case illustrating the syndrome of lower nephron nephrosis, followed for three and a half years, is presented. After severe hemorrhage due to rupture of the uterus at the time of delivery, profound shock occurred. Acute renal failure resulted, as evidenced by oliguria, increasing azotemia, impaired renal concentrating function, and slight hypertension. Urine output began to increase on the second day, and the azotemia decreased after the ninth day.

The effective renal plasma flow (p-aminohippurate clearance), effective glomerular filtration rate (mannitol clearance), and the effective tubular excretory mass ( $Tm_{PAH}$ ) were first measured on the sixteenth postshock day, by

which time a moderate diuresis had been completed, and the blood nonprotein nitrogen had fallen to the upper limit of normal. At this time, the values were approximately 40 per cent of average normal. Clearance measurements repeated thirty-nine days, twenty weeks, forty-one weeks, and three and a half years after the episode of shock showed maximum recovery of filtration rate and plasma flow by the thirty-ninth day, whereas the  $Tm_{PAH}$  became maximal sometime between thirty-nine days and twenty weeks. The maximum values achieved were about 65 per cent of *average* normal. It is not certain whether this indicates that the shock episode resulted in permanent destruction of some renal tissue, or whether the patient's preshock values were at the lower limit of the normal range.

The authors wish to thank Dr. Alexander J. Michie of the Department of Physiology, New York University College of Medicine, for his assistance in several of the clearance studies.

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## **ABDOMINAL MYOMECTOMY: SPECIAL REFERENCE TO SUBSEQUENT PREGNANCY AND TO THE REAPPEARANCE OF FIBROMYOMAS OF THE UTERUS**

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### **Historical Background**

**F**IBROMYOMAS of the uterus develop so frequently during the childbearing years that myomectomy, with its preservation of menstrual and reproductive functions, is the treatment of choice. Modern therapeutic advances such as transfusion, antimicrobial drugs, and asepsis have expanded surgical horizons so that myomectomy is now a safe procedure. This development stands in marked contrast to the earliest myomectomies of a century ago. At first, myomectomy was performed only when the surgeon mistook a pedunculated myoma for an ovarian cyst. Later, myomectomy was preferred to the more formidable operation of hysterectomy.

Martin, in 1890, reported the first series of myomectomies which were performed for the express purpose of conserving uterine function. Eighteen of his 96 patients died. This extremely high mortality rate was no higher than that following hysterectomy at the time. Kelly and Cullen, in 1906, reported the results of 296 myomectomies performed since the opening of the Johns Hopkins Hospital in 1889. There were 16 postoperative deaths. Twelve of the 94 patients with adequate follow-up became pregnant. Victor Bonney became the great advocate of conservative uterine surgery, publishing on myomectomy in 1918, 1922, 1931, 1937, and 1947. His total series numbered 806 cases. He removed 225 myomas in one case and believes that a myomectomy can be performed in all patients and that the decision between myomectomy and hysterectomy should not be based on the anatomical location or number of myomas, but on the spiritual and bodily interests of the patient. W. J. Mayo first wrote on myomectomy in 1911. The series at the Mayo Clinic have been brought up to date in 1920, 1922, 1926, and 1945. The last report covers 250 patients, 101, or 45 per cent, of whom had subsequent pregnancies. Only eight of the 82 patients with a history of sterility became pregnant. Twenty-nine myomectomies were performed during pregnancy. Myomas reappeared in 66 patients, 51 of whom required treatment. Other reports of myomectomy have been published by Alexander, Essen-Moller, Miller, and Weiss. We could find a record of only one case of rupture of the uterus in a pregnancy subsequent to myomectomy. This was reported by Hurd. We have had one similar case in the third trimester of pregnancy, several years after the performance of myomectomy at another hospital. There are without doubt other cases.

### Material

At the New York Hospital from 1932 to 1947, 432 abdominal myomectomies were performed, an average of 29 yearly. Since 3,439 abdominal hysterectomies were performed during this period, the incidence was 1 to 8. All vaginal myomectomies and 158 abdominal myomectomies which were incidental to other operations have been excluded. Two hundred seventy-four myomectomies were suitable for analysis.

When follow-up notes were not available, questionnaires concerning symptoms, subsequent pregnancies, and subsequent operations were sent to the patients with a gratifying response of approximately 50 per cent. Two hundred twelve patients (77 per cent) were followed for two or more years with data available regarding pregnancy and reappearance of myomas (Table I). The remaining 62 patients (23 per cent) had inadequate follow-up.

TABLE I

YEARS OF FOLLOW-UP	TOTAL PATIENTS FOLLOWED	PATIENTS FOLLOWED FOR THIS INTERVAL ONLY
2	212	70
2-4	142	33
4-6	109	34
6-8	75	20
8-10	55	20
10 plus	35	35
		212

The average age was 33.0 years. The highest incidence occurred in the fourth decade (Fig. 1). The youngest patient was 23 years old, the oldest was 55 years of age. Marital status was as follows: married, 221, single, 45, and separated or widowed, 8. The racial distribution was white, 250; Negro, 23 and Mongolian, 1.

Patients with myomas have low fertility. Gravidity was as follows: 150 patients had never been pregnant; 77 had been pregnant once, 29 had been pregnant twice, while only 16 had been pregnant three or more times. Parity was as follows: 192 patients had never had a child, 64 had had one child, while the remaining 18 had had two or more deliveries.

The presenting symptoms are listed in Table II. Pain was the leading complaint. This was distinct from dysmenorrhea and more than mere pressure. Menorrhagia was the second most common complaint. This was due to the myoma in most instances, but other causes, such as polyps and hyperplasia, contributed. Myomectomy was recommended for the large asymptomatic myoma which was detected at routine physical examination.

TABLE II. PRESENTING COMPLAINT

Pain	117	Abortion	30
Menorrhagia	98	Abd. enlargement	29
Infertility	52	Pressure	24
Asymptomatic	43	Dyspareunia	3
Dysmenorrhea	32	Anemia	2

The quickest myomectomy was performed in thirty minutes. The longest required three hours. There were nine myomas, which necessitated entrance into the uterine cavity, several of them because of their submucous locations. The average time of myomectomy was one hour and forty minutes. This is not

unduly long when we consider the meticulous technique, the complete hemostasis, the correction of the position of the uterus, the careful peritonealization, and the fact that many of these operations were performed by members of the resident staff under the guiding assistance of the attending staff.

Table III enumerates the simultaneous operations. There were no complications or unusual fever in the 82 patients who had a simultaneous appendectomy. This is in sharp contrast to the high incidence of intestinal obstruction reported by previous authors.

TABLE III. SIMULANEUS OPERATIONS

Uterine suspension	84	Cervical repair	6
Appendectomy	76	Cauterization of cervix	5
Curettage	53	Salpingostomy	4
Ovarian resection	44	Ant. and post. repair	4
Salpingectomy	8	Amputation of cervix	1
Lysis of adhesions	7	Tubal ligation	1

In 54 cases, curettage was performed at the time of myomectomy. The incidence of postoperative fever and complications was the same as though curettage had not been done. At least 9 of the patients with menorrhagia had a cause for bleeding other than myomas. One patient whose presenting complaint was menorrhagia was treated by myomectomy without curettage only to return two weeks later for curettage because of persistent menorrhagia due to endometrial polyps.

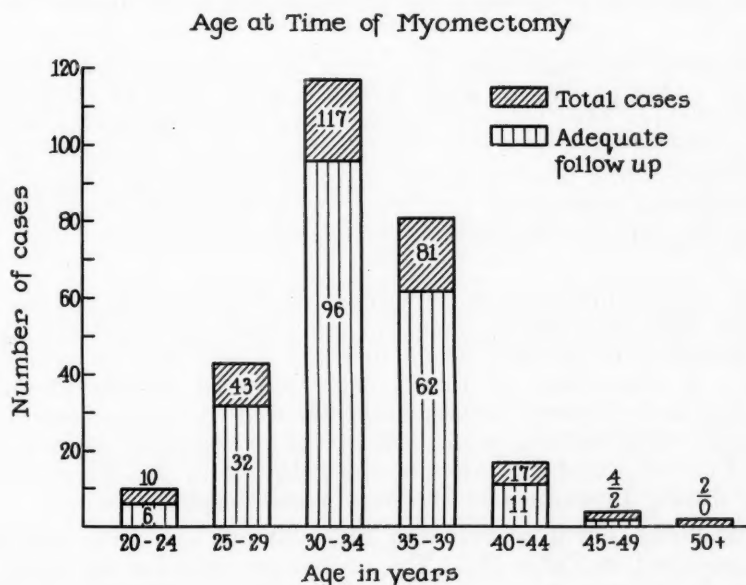


Fig. 1.

The endometrial cavity was opened in 30 patients; 21 of these had menorrhagia. The location of these myomas were: submucous, 9; intramural, 18, and subserous, 3. Of these patients, 13 had febrile postoperative courses. Endocervical drains were used in 4 patients with no influence on the postoperative temperature. Twenty-three patients in whom the cavity was entered, had adequate follow-up; 5 of these had full-term deliveries. Three of these were by

cesarean section, while 2 were by the vaginal route. Five patients had hysterectomy later; 3 for myomas and 2 for menorrhagia, at intervals varying from three to eight years after the myomectomy.

The pathological reports of the endometrium, whether obtained by curettage or by incision into the cavity, were: insufficient tissue or no report, 34; secretory, 30; proliferative, 11; chronic endometritis, 3; endometrial polyps, 3; and hyperplasia, 3. At least 9 of these patients had causes other than myomas to account for their menorrhagia. Curettage, either by the conventional route or in retrograde fashion, is now performed at every myomectomy. The average size of the myomas was 7.0 cm. Forty-eight (18 per cent) were larger than 10 cm. The average number of myomas was three. The number of myomas in 35 cases was more than five.

The distribution of fever postoperatively was: none, 195; one day, 39; two days, 15; three days, 12; three to ten days, 9, and ten to fifteen days, 4. Six of these patients had pyeloureteritis. Two patients developed intestinal obstruction; one on the third day after operation and one a year after the myomectomy. There was one wound evisceration, one wound infection, one pelvic cellulitis, and one pelvic thrombophlebitis. No deaths occurred.

One fibromyosarcoma was encountered in the entire group. This occurred in a 28-year-old woman who had a total hysterectomy performed two weeks after the myomectomy and who has been well during the past two years of observation. The incidence of sarcoma on the basis of patients is 1:274, or 0.35 per cent, while on the basis of the total myomas examined, it is 0.1 per cent. The former figure compares with the reported incidences which range from 0.4 to 2.0 per cent. The possibility of sarcoma may be discounted as a deterrent to myomectomy.

Hystero-graphy was performed in nine patients prior to myomectomy during this study. One patient in whom hystero-graphy with an oil medium had been performed three days prior to myomectomy developed pelvic cellulitis accompanied by fifteen days of fever. The replacement of oil media by aqueous preparations has revived interest in this diagnostic technique. Many such tests have been performed during the past year. They have been especially helpful in the detection of small asymptomatic myomas which have eluded other methods of diagnosis.

Fourteen myomectomies were performed during pregnancy. Six (43 per cent) of these patients aborted, while the remainder were delivered at term. Those who aborted had myomas which involved a considerable amount of the myometrium. A comparison of the myomas removed during pregnancy, at cesarean section, or by cesarean hysterectomy showed the same pathology, necrosis and carneous degeneration, regardless of the presence or absence of symptoms. The study of Child and Douglas in 1943 led to the discontinuance of myomectomy during pregnancy at the New York Hospital.

The pregnancies which occurred in 212 patients who were followed adequately are analyzed in Table IV. The pregnancy rate for the entire group, regardless of desire, was 25.0 per cent. Thirty-four (48.5 per cent) of the 72 patients who were desirous of pregnancy became pregnant, while 39 (51.5 per cent) did not. Nineteen pregnancies occurred in 82 patients whose desire for pregnancy was undetermined, while no pregnancies occurred in 58 patients who did not desire pregnancy. In all, 53 patients were pregnant a total of 80 times. Sixteen (20 per cent) of these pregnancies resulted in abortion. This is the average rate of abortions in the general population, regardless of myomas or myomectomies. Sixty-four (80 per cent) were term deliveries. Eleven of the patients (17 per cent) were delivered by cesarean section. The indication



was previous myomectomy in five, cephalopelvic disproportion in three, elderly primigravidity and sterility in two, and central placenta previa in one. The magnitude of the previous myomectomy influences the decision for cesarean section. The remaining 53 patients (83 per cent) delivered vaginally without event. No transverse presentations occurred; there was one breech presentation. No ruptures of the uterus occurred in the 53 patients who had vaginal deliveries at term. The time interval from myomectomy to the first delivery thereafter is outlined in Table IV. Sixteen (25 per cent) delivered within a year after myomectomy, 36 (66 per cent) delivered within two years after operation, while 48 (90 per cent) delivered within four years.

TABLE IV. INTERVAL FROM MYOMECTOMY TO PREGNANCY

AGE GROUPS	TIME IN YEARS						TOTAL	PER CENT OF NUMBER FOLLOWED
	1	2	3	4	5	6+		
20-24	1						1	16
25-29	4	4				1	9	28
30-34	7	11	7	2	1	2	30	31
35-39	4	5	1	2	1		13	21
40-44								
Total	16	20	8	4	2	3	53	25

Forty-seven patients with primary infertility who were followed adequately deserve special mention. Fifteen of these became pregnant. The remaining 32 did not, but with subtraction of 6 patients in whom previous salpingectomy, tubal occlusion, and azoospermia precluded pregnancy, there were 26 patients (64 per cent) who continued to be infertile. The duration of sterility in the failures and successes was 6.0 and 6.7 years, respectively. The length of follow-up was 3.5 years for the failures and 5.8 years for the successes. The interval from myomectomy to delivery in the successful patients was 1.7 years. The location of the myomas in the patients who failed to become pregnant was intramural in 18 instances and subserous in 14 instances. The patients who became pregnant had a submucous myoma once, intramural myomas 11 times, and subserous 3 times. Twenty-six patients (64 per cent) were still infertile after myomectomy, while 15 (36 per cent) became pregnant; there were 6 abortions and 9 term deliveries. Three of the 5 patients with secondary sterility became pregnant after myomectomy. The average interval to pregnancy was three years (Table V).

TABLE V. PREGNANCY AFTER INFERTILITY

	TOTAL NO. PATIENTS UNCORRECTED	TOTAL NO. PATIENTS CORRECTED	SUCCESSSES		FAILURES	
			NO.	AVERAGE INFERTILITY	NO.	AVERAGE INFERTILITY
Primary infertility	47	41	15	years 6.7	26	years 6.0
Secondary infertility	5	5	2	3	3	3

Previous abortion was the reason for myomectomy in 24 patients. Twelve of the eighteen patients who had aborted once previously, three of the four patients who had aborted twice before, and one of the two patients who had aborted three times previously, became pregnant. It is realized that many of the patients who had aborted only once might have become pregnant without myomectomy.

The time interval of reappearance is tabulated in Table VI. The reappearance rate is 23 per cent. Twenty-four (50 per cent) of these occurred during the fourth to eighth year after operation. Twenty-four (50 per cent) of the reappearances were asymptomatic, while 24 (50 per cent) were symptomatic. Twenty-four hysterectomies were performed during the period of follow-up.

TABLE VI. REAPPEARANCE OF MYOMAS

AGE GROUPS	TIME IN YEARS FROM MYOMECTOMY						TOTAL	PER CENT OF NUMBER FOLLOWED
	0-2	2-4	4-6	6-8	8-10	10+		
20-24			1				1	16
25-29	1		5	3	4		13	41
30-34	1	4	6	5	3	1	20	21
35-39	3	3	2	1	2		11	18
40+	1			1		1	3	25
Total	6	7	14	10	9	2	48	23

### Comment

A conservative philosophy of operating was followed. Incisions were made into the posterior uterine wall when necessary. The endometrial cavity was not entered intentionally. Many patients who in the later years of the study had extensive myomectomies, would have been subjected to hysterectomy in the earlier years. In the earlier years the uterine arteries were temporarily ligated by a soft rubber catheter and the uterus was drained by Penrose drains when the cavity was opened. Both of these techniques have since been abandoned. The current operation is facilitated by the use of Pitocin injected directly into the uterus. This creates an avascular bed which permits ready enucleation of the myoma. The myoma site is closed with several layers of very fine interrupted sutures in inverting fashion. An extensive incision on the posterior wall may be covered by an omental graft, while an anterior wall incision is usually removed from contact with the intestines by suspension of the uterus. Care rather than speed is stressed.

Simultaneous appendectomy has been performed without complication, though former authors thought that it increased the possibility of intestinal obstruction. Appendectomy had not been performed in the single patient who developed mechanical obstruction in the immediate postoperative period.

Curettage can be performed simultaneously without incident. Several patients had menorrhagia caused by polyps, hyperplasia, or chronic endometritis. Myomectomy alone will not cure the menorrhagia in these patients; hence curettage either by the conventional vaginal approach or in retrograde fashion through the wall of the uterus is recommended when menorrhagia is one of the presenting symptoms. The impression was gained that a shallow intramural myoma near the cavity might produce bleeding as readily as a submucous myoma, while a deep intramural myoma near the peritoneal surface will not cause bleeding.

Twenty per cent of these women were operated upon because of infertility and 10 per cent because of spontaneous abortion. The incidence of pregnancy in these two groups, 36 and 66 per cent, respectively, was gratifying. The rate of pregnancy after myomectomy compares favorably with the low parity prior to operation. Since the vast majority of the pregnancies occurred within the first two years after operation, the advice that pregnancy should not be attempted for at least a year after myomectomy, appears to be without foundation. This

is especially true when we consider the average age of the group and the length of infertility in the sterile patients. A shorter period, not to exceed three months, is proposed as a safe interval before attempting pregnancy.

Fewer myomectomies are performed during pregnancy, because most myomas do not cause sufficient symptoms to warrant immediate removal and because of the premature termination of pregnancy which so often follows myomectomy. Torsion of a pedunculated myoma has been the only indication for myomectomy during pregnancy during the past six years. Myomectomy is not performed at the time of cesarean section unless the myoma lies in the line of the incision or is pedunculated. Cesarean hysterectomy is performed for large myomas, while smaller myomas are permitted to remain.

The incidence of pregnancy following myomectomy decreases with the length of the period of postoperative observation, while the rate of reappearance of myomas increases. Though 23 per cent of these patients showed the reappearance of myomas, only half of these had symptomatic myomas which required hysterectomy.

### Summary

Four hundred thirty-two abdominal myomectomies were performed at the New York Hospital from 1932 to 1947; 274 were suitable for analysis, while 212 were followed long enough to determine the incidence of pregnancy and reappearance. The average age was 33 years. These patients have low fertility. The presenting complaints were pain, menorrhagia, and infertility. Many operations, including appendectomy and curettage, were performed simultaneously without complications. Ten per cent of the patients with menorrhagia had a cause for bleeding other than myomas, such as polyps, hyperplasia, or chronic endometritis. One intestinal obstruction occurred in the immediate postoperative period. There were no deaths. One fibromyosarcoma was found in the entire series.

Fifty-three patients became pregnant a total of 80 times, a pregnancy rate of 25 per cent. Fifteen (36 per cent) of the patients with infertility became pregnant after myomectomy. Eighteen (66 per cent) of the patients in whom myomectomy was performed because of previous abortions became pregnant after myomectomy. No ruptures of the uterus occurred. The average interval from myomectomy to delivery was 1.7 years. Twenty-five per cent of the deliveries occurred within the first year after myomectomy. Sixty-six per cent occurred within two years after myomectomy, while 90 per cent occurred within four years.

The reappearance rate is 23 per cent, with the highest number of reappearances occurring during the fifth to eighth year after myomectomy. Half of the patients with recurrences had symptoms sufficient to warrant hysterectomy.

### Conclusions

1. Pain, menorrhagia, and infertility were the leading symptoms of myomas.
2. Curettage can be performed immediately before myomectomy without incident. Curettage is mandatory when menorrhagia is present.
3. Appendectomy can be performed at the time of myomectomy without an increased incidence of intestinal obstruction.

4. Myomectomy is rarely necessary during pregnancy.
5. The pregnancy rate after myomectomy, regardless of the desire of the patient, was 25 per cent, while the rate in those who desired pregnancy was 48.5 per cent.
6. The pregnancy rate in patients with primary infertility was 36 per cent, while the rate in patients with previous abortions was 66 per cent.
7. The abortion rate after myomectomy is 20 per cent. This does not differ too greatly from the incidences which are quoted for the woman without myomas. There was no increased incidence of abnormal presentations. The cesarean section rate of 17 per cent is about five times the clinic average; half of these were performed because of the previous myomectomy.
8. Since the majority of the pregnancies occurred within two years after myomectomy, it is suggested that the interdiction of pregnancy during the first postoperative year is erroneous.
9. The reappearance rate is 23 per cent. Half of these were symptomatic and necessitated subsequent hysterectomy.
10. Myomectomy, while time consuming and requiring more care than hysterectomy, is desirable in younger women, in single women, in women with infertility and repeated abortions, and in general whenever there is a desire to preserve menstrual function and the power of reproduction.

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## BILATERAL POLYCYSTIC OVARIES, STEIN-LEVENTHAL SYNDROME

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**D**URING the developmental phase of surgery the ovary was the frequent victim of operative attack designed to remedy innumerable types of gynecological complaints ranging from vague pelvic pain to almost any type of menstrual disorders. Oophorectomy or excision of ovarian cysts became the common consequences of innumerable exploratory laparotomies undertaken on extremely vague and ill-conceived provocations. Obviously the therapeutic value achieved was practically nil, and, as a result, surgery on the female gonad fell into increasing disrepute.

In 1935, however, Stein and Leventhal<sup>1</sup> called attention to a syndrome which was primarily characterized by amenorrhea and sterility. In essence, they found that the pathological picture of large, pale, polycystic ovaries with thickened capsules was commonly associated with a type of ovarian dysfunction. The results of wedge resection of a portion of the ovaries, in their hands, has been excellent—89 per cent satisfactory results.<sup>2</sup> Meaker<sup>3</sup> has recently reported a series of 65 cases with similar success. The result of this work has been to focus new interest on this remediable defect in ovarian function, and we have attempted to evaluate the cases at the Massachusetts General Hospital.

### Material

In a search of the pathological and surgical files over the past twelve years we have collected 21 cases which have in common the same pathological picture which is similar to that described by Stein in 1939.<sup>2</sup>

The gross appearance of these ovaries is fairly uniform in that each is enlarged two to five times, the enlargement being due to the multiple 0.5 to 1 cm. cysts which crowd the surface of the gonad. Both ovaries are always involved although the degree of enlargement may vary slightly. These ovaries maintain their usual shape. The color of the gonad does vary somewhat, dependent upon the thickness of the tunica albuginea; in some instances, the ovary with the thickest tunica is a pure white with a very smooth, shiny surface. Other ovaries have a mottled white and gray appearance the gray areas are just slightly raised above the surface and are cysts showing through the tunica. The usual ovarian wrinkling is absent, due to the lack of previous ovulation and scarring. No freshly ruptured follicles or corpora lutea are seen.

On cut section the dense tunica albuginea shows up as a thick white layer, as definite as the skin on an apple. The stroma of the ovary is abnormal too, being dense and tough. No buried, yellow, convoluted bodies are seen in the cut section, indicating that there has been no recent ovulation.

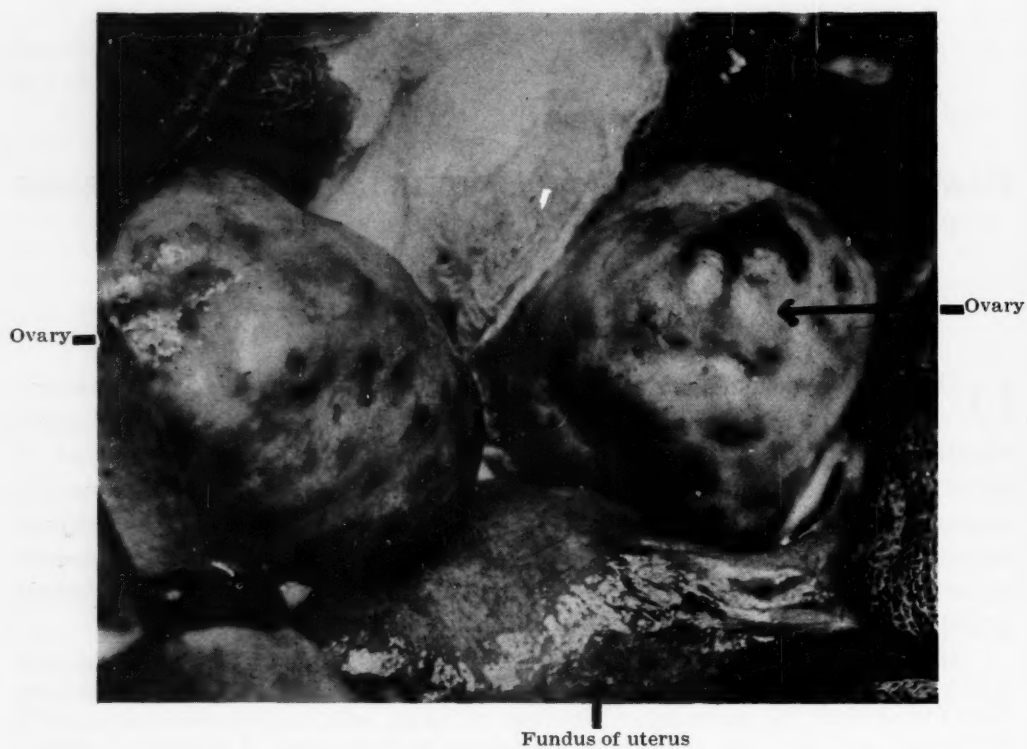


Fig. 1.

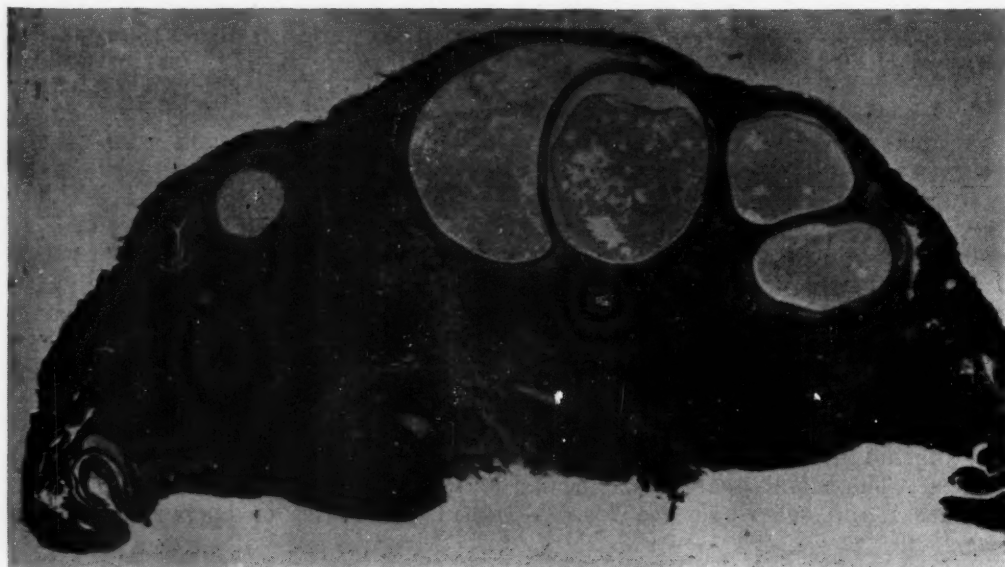


Fig. 2.—Cross section of polycystic ovary.

The microscopic picture invariably shows the thickened tunica albuginea which is a dense collagenous material made up of interlacing lamellae of connective tissue. There are no primordial follicles in this layer but a normal number are found in the cortex. Search through the deeper sections of the ovary will usually fail to show any corpora albicantia, and no corpora lutea are found.

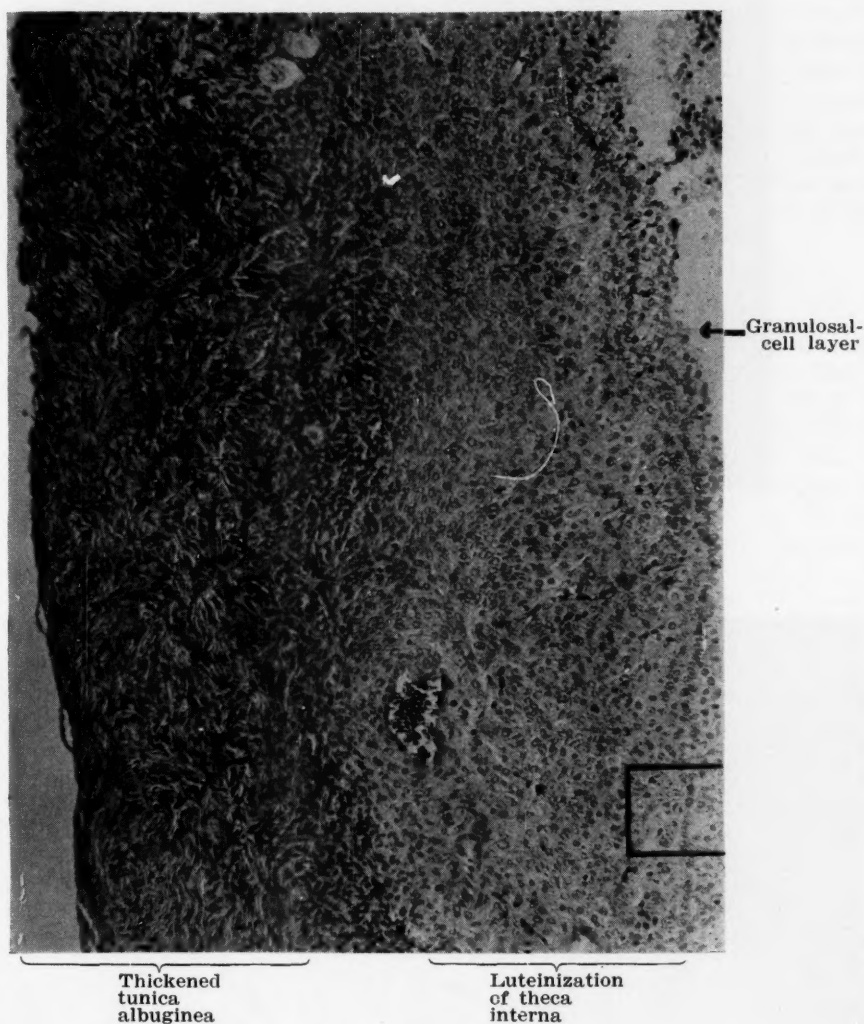


Fig. 3.

Multiple cysts are the striking finding in the slide and they are crowding up against the thickened tunica. The microscopic appearance of these cysts varies greatly and possibly accounts for the varying symptomatology in these women who fail to ovulate. At a glance numerous follicles in all stages of development are seen. Fairly normal ripening Graafian follicles are encountered with a thick layer of granulosa cells, a normal cumulus oophorus and a narrow theca interna and externa, but there are no mature follicles bulging from the surface of the ovary. The follicles appear to mature to some extent and then atresia occurs in one of two ways, either by loss of the granulosa-

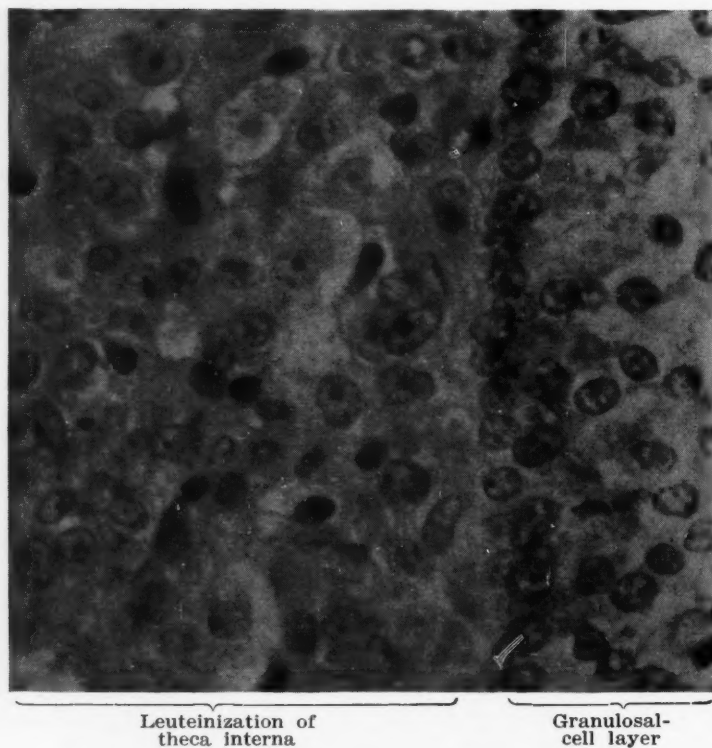
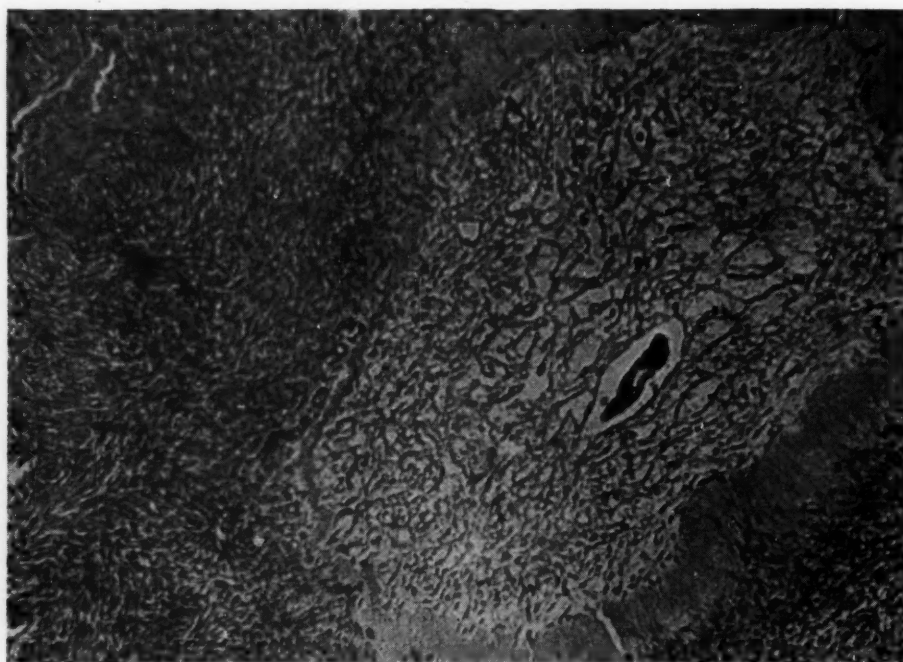


Fig. 4.—High power of Fig. 3.



Tunica albuginea

Atresia folliculi

Fig. 5.



cell layer as in the normal atresia folliculi, or by the formation of cysts lined by normal granulosa cells and showing marked increase in the size and activity of the cells of the theca interna. In the first type the ovum has disappeared, the granulosa layer degenerates and may disappear, leaving only the theca as a wall. These ghost cysts slowly shrink into an amorphous mass of connective tissue called, in their end stage, a corpus fibrosum. The second type of atresia is less common but more interesting because of possibility of hormone production. In these cysts the ovum is absent, the morphologically normal granulosa layer remains and the theca interna is a wide area showing evidence of cellular activity, mitoses, and an increase in the cytoplasm suggesting luteinization. The striking picture is the amount of activity seen in the theca interna. This microscopic picture, which has been called luteinization of the theca interna in unruptured follicles, was first described by Robinson<sup>4</sup> in 1935 in association with metrorrhagia, and has subsequently been noted by Stein<sup>2</sup> in his pathological description of his group of patients suffering from amenorrhea.

### Results

A study of the clinical records and endocrine assays in this group of patients has brought to light a number of interesting problems and has raised considerable speculation as to the etiology and pathogenesis of this pathological entity. Clinically these patients have presented a considerably more varied picture than that originally described in association with this abnormality of the ovary. Amenorrhea or oligomenorrhea was the commonest presenting menstrual disorder and was complained of in 13 of our 21 cases. However, four patients were investigated and operated upon because of excessive uterine bleeding similar to the history cited of V. V. (below). The other four patients gave a history of months of amenorrhea followed by excessive and prolonged menstruation.

CASE 1.—The case history of V. V. (M.G.H. No. 415450) is illustrative of a menorrhagia type of clinical picture. Menarche occurred at 13 years of age, after a normal childhood development. For one year catamenia was fairly regular, then her menses became increasingly profuse and irregular. Over a period of three years she had four hospital admissions because of profuse hemorrhages, occasionally requiring repeated transfusions. There was a marked restriction of normal activity. Because of these recurring profuse hemorrhages, she was followed in the Ovarian Dysfunction Clinic where repeated endometrial biopsies showed only proliferative endometrium. There was temporary improvement following progesterone therapy, but this was very transient, and profuse bleeding occurred the month following the use of the hormone. Her last hospital admission early in February, 1948, was occasioned by excessive uterine bleeding of 25 days' duration. On admission hemoglobin was 8.5 Gm. and the blood smear showed a marked hypochromic anemia; blood platelets, prothrombin, bleeding and clotting times were within normal limits. The basal metabolism rate was plus two. Physical examination was negative except for the physical signs of anemia and large ovaries which were palpable by rectal examination. Secondary sex characteristics showed normal female development. Exploration of the pelvis on Feb. 14, 1948, revealed both ovaries to be enlarged to twice their normal size, and both gross and microscopic examinations were similar to that previously described. Both ovaries were split, everted, and sutured back to back.

Since operation the patient has had an entirely normal menstrual history with menses occurring every 28 to 30 days, lasting four to five days, with normal flow and a few cramps on the first day of bleeding. Endometrial biopsy has shown secretory endometrium for the first time since she was seen in this hospital.

CASE 2.—Another case, that of C. C. (M.G.H. No. 613386), aged 21 years, is illustrative of the syndrome described by Stein and Leventhal, although the microscopic examination of the ovaries is similar to that in the case of V. V. This patient's chief complaints were menstrual irregularities and hirsutism. Menarche occurred at the age of 12 years and menses had always been irregular. In the past few years there had been increasing growth of hair on the face, trunk, and extremities. Physical examination revealed the hirsutism as described and bilateral enlarged ovaries by rectal examination. Secondary sex characteristics were normal and there was no enlargement of the clitoris. The basal metabolism rate, follicle-stimulating hormone, and 17 ketosteroids were all within normal limits. Endometrial biopsy showed proliferative endometrium just prior to menstruation. On April 3, 1948, exploration of the pelvis was carried out and revealed a normal uterus with large, pale, smooth ovaries, both of which had a markedly thickened capsule and contained multiple small cysts. A wedge was removed from both ovaries and the ovarian capsule resutured loosely. Microscopic examination of the ovarian sections showed multiple follicle cysts with marked activity of the theca interna. Since operation menses have been entirely normal and regular, occurring every 32 days, with a normal flow and occasional cramps. Endometrial biopsy has shown secretory endometrium. The hirsutism has been unchanged but there has been no evidence of progression.

These two cases are illustrative of the fact that a normal menstrual cycle can be established by a simple plastic operation in young women who have apparently infrequently ovulated in the past and whose ovaries show this abnormal collagenous thickening of the tunica albuginea and multiple cysts. The results have not been so successful in all the cases, however, as in these two.

Various types of surgery have been performed in this group of cases. In the early years of the investigation of hirsutism, two patients with symptoms which we now feel to be fairly typical of the Stein-Leventhal syndrome each had an exploratory laparotomy and a small ovarian biopsy taken before bilateral adrenal exploration. This we consider inadequate surgery since neither patient did well, yet the pathological picture was definitely that of sclerotic, polycystic ovaries. Stein<sup>1</sup> has advocated a wedge resection of one-half to three-fourths of the ovary with resuture. This procedure was employed in thirteen of our group, while six had the ovary split and sutured back to back, as described by Bailey.<sup>5</sup> The results of the various types of surgery have been classified as follows: excellent if a completely normal menstrual cycle has followed surgery and if pregnancy has ensued, good if there have been only minor menstrual irregularities following surgery, fair if only minor improvement occurred in the presenting complaint, and failure if no improvement followed surgery. In the group with adequate surgery six had excellent results; seven, good results; five were classified as fair; and in one case the operation failed. The result was satisfactory in 68 per cent, as compared to 89 per cent improved, as reported by Stein. One of the patients with severe menorrhagia failed to improve following splitting of the ovary and after four years of hormonal and other treatment had a hysterectomy. The ovaries were full of cysts and the tunica was markedly thickened at the time of the second operation. Two of the patients with unsatisfactory results showed persistently low basal metabolism rates; one has failed to follow any consistent therapy with thyroid hormone; the other has not responded to thyroid therapy.

#### **Etiology and Hormonal Studies**

With the evidence available at present, the etiology of this particular type of ovarian dysfunction and the pathogenesis of the histological changes in the ovary remain obscure. Stein feels that the etiology of this disorder is

primarily a hormonal imbalance with overactivity of the pituitary resulting in polycystic ovaries. He feels that the fibrosis of the ovarian capsule occurs because of thickening of the germinal epithelium over the multiple follicle cysts.

Very few endocrinological assay studies have been performed by Stein or others. This group of cases has been studied under the direction of Dr. Fuller Albright and we are able to report on his 17-ketosteroid determinations and follicle-stimulating hormone assays done quantitatively after his modification of the Heller and Heller technique.<sup>6</sup> By this technique the excretion of the F.S.H. per 24 hour period can be accurately determined and is reported as so many mouse units per 24 hours, the normal values being 6.5, 13 to 26. Values of 96, 192 or above are elevated, as is commonly found during the menopause. We can report that twelve patients had an F.S.H. determination and in every instance the F.S.H. production was within normal limits as given above. This observation casts some doubt on the suggestion of Stein that an increased excretion of anterior lobe of the pituitary gland accounts for this syndrome. Of course only F.S.H. was tested for in this work and as yet no accurate determination of the L.H. (luteinizing hormone) has been developed. Zondek<sup>7</sup> has shown that stimulation with large doses of anterior pituitary lobe hormones may cause either uterine bleeding or amenorrhea and if continued over a long period of time eventually results in histological changes in the ovaries. These ovaries have multiple follicle cysts, a thickened capsule, and increased fibrosis of the stroma. The cysts may have either granulosa cells only or theca cells—a picture which approaches that seen in the Stein-Leventhal syndrome. Possibly this pathological picture is due to excessive L.H. or some other unknown hormone, but certainly the F.S.H. is normal.

Bailey<sup>5</sup> reported on a series of seventeen patients with amenorrhea and this same pathological picture. He postulated that the amenorrhea was due to a basic hormone deficiency resulting in lack of follicle ripening and ovulation. This he felt led to a condition of multicystic disease in the ovaries. This suggestion of hormone deficiency seems to us more likely, the deficiency being in luteinizing hormone production. Multiple follicles are stimulated to start toward maturity but the necessary push through to ovulation, thought to be due to L.H., is lacking, so that groups of follicles begin to undergo atresia and another group starts to develop. This process goes along until finally the ovary is crowded with follicles in all stages of development and atresia. The fibrosis of the capsule may be a secondary change in the ovary.

Hirsutism occurred in nine of our twenty-one patients, which is approximately the 50 per cent incidence quoted by Stein<sup>8</sup> in his series of fifty-three cases. The degree of hirsutism varies from slight to severe and is noted particularly in those with amenorrhea rather than menorrhagia. Hirsutism is not easy to explain but then neither is the hirsutism that occurs in so many otherwise entirely normal and feminine women. The possibility that there might be some associated adrenal abnormality or androgen tumor led us to determine the 17-ketosteroid output in nine patients in this series, and in no instance was there an increase over the normal feminine level. Perhaps the mechanical disorder in the ovary results in a shift in the estrogen-androgen balance which we are unable to measure accurately at present.

Basal metabolism tests have been done on all of the patients and in only two patients was the basal metabolism rate below 20. We have not been able, therefore, to demonstrate any hormonal imbalance with the endocrinological studies available at the moment.



Since we cannot prove an endocrine imbalance as the etiological factor in this syndrome, we must consider a number of facts which would support the thesis that the collagenous infiltration of the ovarian capsule might be the basic disorder. These facts are as follows: The majority of the patients respond immediately and rapidly to the removal of the mechanical barrier to ovulation. These patients stay well. There have been no recurrences in those patients in whom a good result was obtained. The failure to demonstrate any basic hormonal imbalance by endocrinological studies favors a mechanical theory. Also, rarely ovulation does occur, apparently when a follicle manages to penetrate the barrier. The fact that the clinical symptoms and signs do not appear immediately after the menarche is not an argument against the mechanical theory. In fact, we might expect a succession of anovulatory cycles until the accumulation of follicle cysts within the capsule became sufficient to cause a progressive increase in the degree of ovarian dysfunction.

With the evidence at hand the etiology is obscure. We feel that the two most likely possibilities are: (a) a congenital fibrosis and thickening of the ovarian capsule which result in a mechanical barrier to ovulation and resulting polycystic changes in the ovaries or (b) a primary hormonal imbalance, possibly in the secretion of LH by the pituitary with secondary changes, as described in the ovaries. We are unable to favor one over the other with the evidence available at present.

### Diagnosis

The clinical picture associated with this pathological disorder of the ovary presents such a variable constellation of symptoms and signs that no specific syndrome can be described as typical. The rarity of this pathological entity (twenty-one cases in twelve years) and the frequency of menstrual irregularities in young women make it essential that a set of criteria be fulfilled before subjecting a patient to pelvic exploration.

1. The presence of persistent failure of ovulation should be established by basal temperature charts and endometrial biopsies.

2. Other specific endocrine disorders should be ruled out. Basal metabolism rate, follicle-stimulating hormone, and 17-ketosteroids should be within normal limits. In borderline cases more extensive endocrinological investigations may be advisable.

3. The presence of bilateral enlarged ovaries should be established if possible in one of the following ways:

- a. *Physical examination*, in six of the 21 cases, the enlarged ovaries were palpable by pelvic or rectal examination.

- b. *Culdoscopy*, which in general is restricted to married women, will give a direct visualization of the typical, large, pale, smooth ovaries.

- c. *Gynecography* or *pneumoroentgenography* of the pelvis has been utilized very successfully by Stein in demonstrating an abnormal ratio in the relative sizes of the ovaries and uterus. We have had no experience with this technique.

These diagnostic criteria are extremely important in order to prevent a return to the era when ovarian plastic operations were undertaken so lightly and ill-advisedly and with such uniformly poor results.

### Treatment

Once the diagnosis of fibrosis of the ovarian capsule with bilateral polycystic ovaries has been established, there is no question but that the treatment is surgical. Hormonal therapy has been uniformly unsuccessful.



While a number of plastic procedures (wedge resection, splitting and eversion, decapsulation, culdoscopic resection) have been utilized, the most physiological would seem to be one which entails a wedge resection of both ovaries, puncturing the multiple cysts and loosely resuturing the capsule. This simple and satisfactory technique has already been described in detail by Stein (1945).<sup>8</sup>

### Conclusions

1. A specific entity, polycystic ovaries with a thickened tunica albuginea, exists and is associated with a variable clinical syndrome.
2. The abnormality is remediable by any one of several ovarian plastic operations, the most satisfactory of which is bilateral wedge resection with resuture of the capsule.
3. The pathological entity is relatively rare, and while widespread recognition of its existence may bring to light more cases, it is not to be inferred that ovarian plastic procedures will benefit any but a relatively small percentage of the menstrual disorders.

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264 BEACON STREET.

## **RENAL HEMODYNAMICS IN THE TOXEMIAS OF PREGNANCY**

### **Alterations of Kidney Function by Regional Nerve Block\***

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IT LONG has been known that there is a disturbed water balance in the toxemias of late pregnancy.<sup>1, 2, 3</sup> Clinically this disturbance is manifested as excessive weight gain, edema, oliguria, and, in severe cases, as anuria.

As the maintenance of fluid balance is a principal function of the kidney, an investigation of renal physiology should contribute to the search for causative factors of the water retention which is so characteristically present in the toxemias.

By means of the modern clearance methods of studying kidney function, as perfected by Homer Smith<sup>4</sup> and his co-workers, one is now able to evaluate various aspects of renal physiology as altered by disease processes. The efficacy of therapeutic measures aimed at correcting these processes may also be appraised by these same measures.

### **Kidney Function in Normal and Toxic Pregnancy**

In uncomplicated pregnancy it has been shown that the various aspects of renal function are unaltered from the normal.<sup>5</sup> In the toxemias of late pregnancy, however, several alterations have been noted. Glomerular filtration rate is usually lowered.<sup>5-9</sup> Renal blood flow remains normal, but renal resistance is increased. Filtration fraction is somewhat decreased. It has been postulated that spasm of the afferent arteriole could be one explanation of these findings and further account for the decreased urine flow in certain cases.<sup>5</sup> Decreased glomerular filtration rate could also result from a thickening of the capsular membrane. It would have to be postulated that this thickening is a reversible process, for in those cases of toxemia where elevated blood pressure subsides after delivery, the glomerular filtration rate returns to normal levels.

Water retention would be favored by an increase in the amount of circulating antidiuretic hormone during pregnancy. Chesley has recently been able to demonstrate an antidiuretic principle by the slow perfusion of placental tissue rendered ischemic in the Lindbergh pump. He postulates that a similar tissue ischemia might be present in the placentas of toxemic patients.<sup>10</sup> Ham and Landis<sup>11</sup> have demonstrated an antidiuretic principle in the placentas of patients with eclampsia and severe pre-eclampsia. It is distinguishable from the antidiuretic hormone of the pituitary.

In eclampsia and severe pre-eclampsia there is every evidence of a generalized constriction of the arterioles. A study of the eyegrounds in these

\*Aided by a grant from Eli Lilly and Company.

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patients reveals varying degrees of spasm of the retinal vessels.<sup>12</sup> Electroencephalographic tracings show wave changes in the eclamptic which have been interpreted as being the sequelae of temporary vascular occlusion.<sup>13, 14</sup> The extremities are found to be cool, and the patient is extremely susceptible to the cold pressor test.<sup>1, 13</sup> It would follow that this angiospastic process also prevails in the kidney.

Several workers, appreciating the disturbed vascular physiology in the severe toxemias, have postulated that neural constriction of the afferent arteriole accounted for the oliguria and anuria frequently present in these patients.<sup>13, 15</sup> It was on this basis that regional nerve block was suggested as an effective means of overcoming the decreased urine flow. By blocking the renal nerves the spastic constriction of the afferent arteriole should be relieved. Further, it was reasoned, this should result in an increased glomerular filtration rate and thereby a diuresis. To lend weight to these assumptions there have appeared in the literature of the past several years scattered reports of beneficial results from this type of therapy.<sup>16, 17</sup>

### Material

In an effort to evaluate critically the influence of regional nerve block on renal hemodynamics, a group of fourteen patients with eclampsia or severe pre-eclampsia was studied. Renal clearance values for mannitol and para-aminohippurate were determined both before and during nerve block. In each case determinations were made for glomerular filtration rate, renal blood flow, tubular secretion, filtration fraction, and renal resistance.

Of the original group, five cases were discarded because of a questionable diagnosis of pure pregnancy toxemia or because of technical difficulties encountered during the running of the tests. Of the nine cases completely studied five were eclampsia and four severe pre-eclampsia.

### Studies of Glomerular Filtration

Using mannitol as the testing agent, glomerular filtration rate was determined soon after hospital admission and later after instituting a continuous caudal or a continuous spinal block. The interval between the time of starting the block and the time that the tests were run was varied from one to twenty-two hours. In each case the anesthetic agent used was Metycaine 1.5 per cent.\* The cutaneous level of analgesia was maintained at thoracic 6 or above.

TABLE I

PATIENT	DIAGNOSIS	MEAN BLOOD PRESSURE		GLOMERULAR FILTRATION RATE*	
		BEFORE BLOCK	UNDER BLOCK	BEFORE BLOCK	UNDER BLOCK
1	Eclampsia	133.5	106.5	76.4	55.8
2	Pre-eclampsia	152.3	137.9	102.0	79.0
3	Pre-eclampsia	119.4	103.9	77.0	65.2
4	Eclampsia	123.8	104.2	129.5	88.8
5	Eclampsia	154.4	104.4	76.5	50.0
6	Eclampsia	115.2	133.4	58.8	62.8
7	Eclampsia	111.8	114.4	77.3	96.5
8	Pre-eclampsia	137.7	128.3	117.0	66.0
9	Pre-eclampsia	143.8	127.0	84.6	50.8

\*Expressed as cubic centimeters per minute.

\*Metycaine (Gamma-[2-methyl-piperidino] propyl benzoate hydrochloride, Lilly).

In seven of the nine cases the glomerular filtration rate was below normal originally. Of two patients with normal values one was an eclamptic and one a severe pre-eclamptic. Following regional nerve block the filtration rate was lowered in seven cases, an average of 27.7 per cent.

In two cases the glomerular filtration rate was slightly increased under block. It is significant that these are the two cases in which the mean blood pressure was not lowered by nerve interruption. The first experiment was run in each instance with the patient under heavy sedation. In the uncooperative eclamptic patient, sedation of a certain degree is necessary to carry out a technically valid experiment. The resulting blood pressure levels were lower than those attained during the second test in which sedation was light, and the blood pressure was being controlled chiefly by means of the regional nerve block.

Because the glomerular filtration rate varied directly with mean blood pressure, an attempt was made to prevent a fall in filtration rate under block by preventing the fall in blood pressure. A third experiment was carried out in one case, and an attempt was made to maintain the blood pressure by the intramuscular injection of 50 mg. ephedrine sulfate. It has been shown that the injection of this amount of the vasopressor will not result in a constriction of the renal arterioles.<sup>4</sup> This expedient resulted in a slight but probably insignificant increase in the filtration rate. This second value for filtration rate was still below that recorded prior to nerve block, however.

TABLE II

MEAN BLOOD PRESSURE			GLOMERULAR FILTRATION RATE		
BEFORE BLOCK	UNDER BLOCK	EPHEDRINE WITH BLOCK	BEFORE BLOCK	UNDER BLOCK	EPHEDRINE WITH BLOCK
137.7	128.3	130.4	117.0	66.0	78.5

It should not be concluded from this one experiment that glomerular filtration rate cannot be increased by regional nerve block, however. It is noted that the mean blood pressure in this case under ephedrine and nerve block is still below the original pre-block level. Attempts to encourage kidney function in this manner would of necessity negate the other beneficial effects of the block, i.e., the reduction of blood pressure with its apparently desirable sequelae.

### Studies of Renal Plasma Flow

Renal plasma flow was determined in all cases by determining the para-aminohippurate clearance. Five of these toxemic patients had a plasma flow

TABLE III

PATIENT NUMBER	RENAL PLASMA FLOW*		TUBULAR SECRETION†		FILTRATION FRACTION‡	
	BEFORE BLOCK	UNDER BLOCK	BEFORE BLOCK	UNDER BLOCK	BEFORE BLOCK	UNDER BLOCK
1	538	302	48.7	45.7	14.2	18.5
2	650	635	45.0	46.0	15.0	12.4
3	456	367	66.0	37.8	16.8	17.8
4	642	636	66.2	75.4	20.2	13.9
5	318	385	16.9	16.9	24.0	13.0
6	635	322	62.5	57.2	9.3	19.5
7	608	608	39.8	33.8	12.8	15.9
8	1115	597	65.3	86.0	10.5	15.8
9	443	835	30.7	55.0	19.1	6.8

\*Expressed as cubic centimeters plasma flow per minute.

†As milligrams para-aminohippurate secreted by the tubules per minute.

‡Expressed as per cent plasma contributing to the formation of the glomerular filtrate.



within normal limits on the first experiment. Two values were slightly reduced, and one was definitely below normal. In only one case was an increased plasma flow noted.

There seemed to be no consistent change in the renal plasma flow as the result of regional nerve block. In three cases the flow was unaltered; in four it was reduced, and in two it was increased.

### Studies of Tubular Secretion

Of the nine cases, five showed an initial reduction in tubular excretory capacity measured by tubular maximum para-aminohippurate. The remaining four fell within the lower limits of normal. The tendency, then, was for the tubular secretion to be lower than average in all cases. This observation in toxemic patients has not been reported previously. Tubular saturation was assured by determining the load/tubular maximum ratio which was shown to be adequate in each experiment.

Following regional nerve block there was no significant alteration of tubular activity in six cases. There was an increased value in two and a slight reduction in one (Table III).

### Filtration Fraction

Normally about 20 per cent of the plasma presented to the glomerulus is filtered during its passage through the kidney. Filtration fraction values in these nine cases were normal in three. The remaining six were below normal, with four of the six significantly reduced. Four patients showed an increase in filtration fraction under regional nerve block; four showed a decreased fraction, and one remained unchanged. As the result of nerve block there is nothing to suggest an alteration in the caliber of the glomerular efferent arteriole.

If regional nerve block techniques actually improve kidney function by relieving intrarenal angiospasm and in particular by relieving spasm of the afferent arteriole, these changes should be reflected in a reduction in the renal resistance.

Of the nine cases completely studied, seven showed renal resistance values above the normal. This suggests afferent arteriolar constriction or obstruction as a cause of this increased resistance when considered in the light of a little-altered filtration fraction. In other words, the renal resistance was considered to be increased out of proportion to the decreased filtration fraction.

TABLE IV

PATIENT NUMBER	RENAL RESISTANCE		MEAN BLOOD PRESSURE	
	BEFORE BLOCK	AFTER BLOCK	BEFORE BLOCK	AFTER BLOCK
1	191	246	133.5	106.5
2	168	157	152.3	137.9
3	170	193	119.4	103.9
4	143	130	123.8	104.2
5	356	199	154.4	104.0
6	119	254	115.2	133.4
7	136	140	111.8	114.4
8	88	159	137.7	128.3
9	233	107	143.8	127.0

Following nerve block, the renal resistance was increased in four cases, decreased in two, and unaltered in three cases. In the four cases where the renal resistance was increased, the filtration fraction was concomitantly increased. This indicates constriction of the efferent as well as the afferent ar-

teriole. In the two cases in which resistance was decreased by block the filtration fraction was also decreased, further suggesting activity in the same direction by the afferent and efferent vessels.

Mean blood pressure was reduced by regional nerve block in all but two cases. The preliminary run in each of these two was carried out under heavy sedation as mentioned above. During the run under nerve block the patient was little sedated with a resulting higher blood pressure value which was, however, still well below the admission level. Of the seven patients in whom blood pressure was lowered, an average reduction of 21.8 mm. occurred as the result of nerve block. Mean blood pressure was determined by the formula:

$$\text{Diastolic pressure} + .44 (\text{systolic pressure} - \text{diastolic pressure})$$

### Comments

It would seem from this project that regional nerve block is of little or no value, so far as the kidney is concerned, in the treatment of the severe toxemias of late pregnancy. It is apparent that the generalized relief of angiospasm below the level of block is such that a reduction of blood pressure nearly always results. This reduction of systemic blood pressure is sufficient to reduce the effective filtration pressure to the kidney to the point that glomerular filtration is reduced thus negating any beneficial effect which might result from the specific relief of angiospasm in the afferent arteriole.

We do have evidence, however, that angiospasm of the afferent arteriole is present in this group of toxemic patients as reflected by the increased renal resistance in the majority of cases. Contrary to expectation, nerve block decreased resistance in only two cases. These lowered values, however, were still above the normal. This would indicate that *the afferent arteriole is not under complete neural control in eclampsia and severe pre-eclampsia*. This evidence points to humoral constriction, especially so when it is seen that nerve block causes increased renal resistance in some cases. These findings are in agreement with those of Mokotoff and Ross,<sup>19</sup> who recently reported the effect of spinal anesthesia on renal function in patients with congestive heart failure.

The explanation of the reported relief of oliguria and anuria by regional nerve block might be the result of the so-called pavex effect of an alternating blood pressure. We have noted better responses in urine flow in those cases where the blood pressure is alternately lowered and raised than in those where it is constantly kept at a low level.

The fact that regional nerve block does not affect the kidney as originally thought does not detract from its usefulness in the treatment of the severe toxemias of pregnancy. By means of these conduction techniques a critical hypertension *can* be lowered and controlled over a period of days. It is reasonable to assume that this reduction of blood pressure will result in a decreased incidence of intracranial vascular accidents. Nerve block will also bring about a dramatic response in the patient with acute left ventricular failure. These two complications have accounted for all the deaths in a series of cases from this department over the past three and one-half years. Uremia in the eclamptic is frequently a sequela of obstetrical hemorrhage and shock rather than of toxemia. The resulting damage to the kidney may affect the tubules producing the picture of the so-called lower nephron syndrome. Regional nerve block could offer little in correcting tubular damage of this type.

### Comments on the Etiology of Eclampsia in the Light of the Present Study

Evidence points to the conclusion that eclampsia is a disease resulting from a disturbed physiology of principally the liver and certain endocrine glands.

Hofbauer<sup>2</sup> has made an excellent summary of his and other investigators' findings in a recent publication to substantiate the contention that the lack of certain antagonistic substances to the secretions of the posterior pituitary gland is the starting point of the train of events which leads to the clinical manifestations of the toxemic state. He believes that liver damage results from certain split protein fractions arising from syncytial buds which have broken off into the maternal circulation from the placenta. The liver being damaged is unable to detoxify the products of the posterior pituitary which, in turn, appear in the blood stream in relatively high concentrations. The phenomenon of generalized arteriolar constriction is thought to be a manifestation of increased vasopressin stimulation.

The oliguria of eclampsia may be explained on the basis of decreased glomerular filtration (as the sequelae of angiospasm) or as the result of an increased amount of circulating antidiuretic hormone of the pituitary.

Among those who support the dietary deficiency theory of etiology, it is just as reasonable to assume that the original liver impairment is the result of nutritional and vitamin inadequacies. From this point on the chain of events is the same.

The present study would tend to substantiate the biological concept of the etiology at several points. First, it was shown that glomerular filtration was below normal in the majority of patients. Second, it was found that these patients had abnormally high values for renal resistance. These two findings would point to constriction of the afferent glomerular arteriole as the causative factor. Constriction of this arteriole might result from an abnormally large amount of circulating pressor principle. That a humoral agent is responsible for the constriction is suggested by the fact that the afferent arteriolar tone could not be reduced by regional nerve block. However, this finding also could be explained on the basis of endothelial proliferation with thickening of the endothelium of the afferent arteriole as well as that of glomerulus as reported by Fahr.<sup>18</sup>

### Summary and Conclusions

1. The observation that glomerular filtration rate is decreased in the majority of patients with severe toxemia of late pregnancy is confirmed.
2. The hypertension of eclampsia and severe pre-eclampsia can be reduced and controlled by means of continuous regional nerve block. The combination of moderate sedation and nerve block is even more effective in controlling blood pressure than either one alone.
3. Concomitant with the lowering of the mean blood pressure by block there is a reduction of the glomerular filtration rate.
4. There is no consistent alteration of the renal plasma flow in eclampsia and severe pre-eclampsia. Plasma flow is not characteristically changed by continuous nerve block.
5. Tubular secretion is decreased somewhat in toxemic patients. Secretory capacity of the tubules is unaltered by therapeutic nerve interruption.
6. The severe toxemias of late pregnancy are characterized by a decrease in the filtration fraction from the normal.
7. Renal resistance is increased in eclampsia and severe pre-eclampsia. The associated reduction in filtration fraction suggests that the cause for the

increased resistance lies proximal to the glomerulus and probably represents afferent arteriolar constriction. Regional nerve block did not reduce renal resistance in the majority of cases studied.

8. Various forms of regional nerve block remain important therapeutic tools in the management of the severe pregnancy toxemias. Their effectiveness in overcoming oliguria and anuria has been overemphasized. The occasional reported dramatic response may well be purely coincidental to the spontaneous re-establishment of urine flow.

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# THE ESTIMATION OF FETAL MATURITY BY ROENTGEN STUDIES OF OSSEOUS DEVELOPMENT

## Preliminary Report

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**A**N ACCURATE determination of the maturity of the fetus frequently assumes paramount importance in the proper management of the gravid woman. The estimation of intrauterine age most often presents a problem when induction of labor or elective cesarean section is indicated. Since neonatal risk materially decreases if the fetus is mature at the time of delivery, every effort compatible with safety of the mother should be made to terminate pregnancy only at a time when the infant is physiologically prepared for extrauterine life.

Unfortunately, the commonly employed methods of determining the estimated date of confinement, based on menstrual history, date of fruitful coitus, quickening, uterine measurements, and fetal encephalometry, leave much to be desired. Radiological examination of the osseous development of the fetus constitutes another and perhaps a more reliable means of estimating physiologic fetal age.

The appearance of ossification centers of the distal epiphysis of the femur and of the proximal epiphysis of the tibia at approximately the time the fetus reaches maturity and the possible use of these centers as indicators of maturity have been discussed by several authors.

TABLE I.<sup>1</sup> PERCENTAGE OF ROENTGENOGRAMS OF NEWBORN INFANTS IN WHICH PRESENCE OF CENTER WAS CLEAR FOR VARIOUS WEIGHT GROUPS (GRAMS)

CENTER OF OSSIFICATION, RACE, AND SEX	BIRTH WEIGHT IN GRAMS					
	LESS THAN 2,000	2,000- 2,499	2,500- 2,999	3,000- 3,499	3,500- 3,999	4,000 OR MORE
	PERCENT- AGE	PERCENT- AGE	PERCENT- AGE	PERCENT- AGE	PERCENT- AGE	PERCENT- AGE
<i>Distal epiphysis of femur.—</i>						
White boys	9.1	75.0	85.3	100.0	100.0	100.0
White girls	50.0	91.7	98.0	100.0	100.0	100.0
Negro boys	18.2	88.5	90.7	94.0	100.0	100.0
Negro girls	50.0	93.8	99.0	100.0	100.0	100.0
<i>Proximal epiphysis of tibia.—</i>						
White boys	0.0	18.8	52.9	78.8	84.1	97.1
White girls	0.0	54.2	75.5	85.7	90.7	90.5
Negro boys	0.0	38.5	62.7	76.0	80.0	92.9
Negro girls	14.3	40.6	76.7	88.1	86.4	100.0

In a study of 1,112 newborn infants at Johns Hopkins University, Christie found that the proportion of infants having each of several centers of ossification increased with birth weight. He demonstrated that there were race and sex differences in osseous development which corresponded to the greater maturity of female infants as compared with male infants and of Negro infants as compared with white infants of equal weight. Data from this study are reproduced in Table I. It is seen that the distal epiphysis of the femur, usually appearing by the thirty-sixth gestational week, was present in most infants weighing over 2,500 grams, so that its absence probably indicates an immature or just barely mature infant. The proximal epiphysis of the tibia develops somewhat later (appearing by the 39th to 40th week) and was found in only two infants (both Negro females) weighing under 2,000 grams. Thus, its presence is indicative of a mature or nearly mature infant. Whereas there is individual variability in the development of these centers, they appear to be fairly good indices of maturity, particularly if size of the center, as well as its presence or absence, is taken into account. Also, since birth weight is not perfectly correlated with physiological maturity, it may be that the relation between presence or absence of these centers and physiological maturity is somewhat better than their relation to birth weight would indicate. Certainly the variation in the appearance of the centers with sex and race is consistent with well-recognized differences in maturity by sex and race within similar weight groups. It was felt that an evaluation of the method on a series of roentgenograms of fetal parts was needed, and the present study was undertaken to determine whether the estimates so obtained were sufficiently valid to be useful.

### Method of Study

#### *Technical Factors Used for Fetal Roentgenography.—*

For fetal studies in Vanderbilt University Hospital an anteroposterior and a right anterior oblique roentgenogram are made initially and processed immediately. The films are then examined to see if the desired areas can be visualized. If additional views are necessary, a left anterior oblique projection is made and a lateral view is also used. In this projection a wedge-shaped aluminum filter is utilized, the thin side of the filter being directed toward the maternal spine in order to overcome the increase in density in this position. In all the exposures 14 by 17 inch films are used.

During the last few weeks of pregnancy the patient may be too uncomfortable to maintain the left anterior or right anterior oblique positions. If this occurs, the right and left posterior oblique projections are used.

The milliamperereconds best suited for fetal roentgenography at 36 in. focal-film distance are as follows:

- 90 milliamperereconds for anteroposterior view.
- 105 milliamperereconds for oblique views.
- 135 milliamperereconds for lateral views.

The above milliampererecond factors are correct when exposures are made using the moving grid.

The part thickness of the patient is used to determine the kilovolts selected, employing the basic formula: kilovolts =  $2 \times$  part thickness in centimeters + 27 when par speed screens and standard brand films are used.

### Description of Data

For this study, one hundred such roentgenograms were reviewed. These had been taken for any one of a variety of reasons during pregnancy. The cases studied thus represent cases selected because some problem presented itself dur-

ing pregnancy, the solution of which depended somewhat upon an accurate determination of fetal maturity. All of the patients in the present study were white.

The following items were recorded from the roentgenograms alone, without reference to information in the histories of the patients:

1. The presence or absence of the distal epiphysis of the femur and of the proximal epiphysis of the tibia.
2. The estimated weight of the fetus.
3. The estimated number of weeks of gestation.

Then, as a basis for evaluation, the following information was taken from the histories of the mother and baby:

- a. The weeks of gestation at the time of the roentgenogram as calculated from the menstrual history.
- b. The weight and length at birth.
- c. Any statement that was given in the history about the physiological maturity of the infant at birth.

Unfortunately, none of the latter is a completely satisfactory measure of maturity of the fetus at the time of the roentgenogram. Menstrual history is frequently unreliable. The interval from the roentgenogram to birth varied from a few hours to ninety days; thus b and c were not always directly applicable. Also, weight and length are not perfectly correlated with maturity. Moreover, statements about maturity at birth are quite subjective in character.

The weight of each fetus at the time of the roentgenogram was estimated from the birth weight by deducting from the latter an amount equal to the estimated average gain in weight of fetuses during the interval from roentgenogram to birth. Length at the time of roentgenogram was estimated in a similar way. A study of gains in weight of fetuses reported in the literature revealed quite divergent estimates of weight gains. An average of the values given by Scammon and Calkins<sup>2</sup> and by Streeter<sup>3</sup> yielded the following, which were used:

LUNAR MONTH	AVERAGE GAIN PER DAY (GRAMS)
8th	21
9th	26
10th	30

There was much better agreement on the reported gains in length during the fetal period, most authors reporting a gain of about 5 cm. per lunar month, and this is the estimate used. It should be recognized that these figures are based on fetuses delivered prematurely, and also that individual fetuses will vary from the average figures. The interval between the roentgenogram and birth was seven days or less in 55 per cent of our cases, and was fourteen days or less in 64 per cent. The error in estimating weight and length at the time of the roentgenogram is believed to be relatively small when the interval is less than two weeks. The interval between the roentgenogram and birth was over thirty days in 14 per cent, and in these the error in estimating weight and length at the time of the roentgenogram may be considerable.

### Results

We shall first show the relation between presence or absence of the centers and each of the three criteria of maturity at the time of roentgenogram: weight, length, and period of gestation. The accuracy of the quantitative estimates of weight and gestation based on the roentgenogram will then be discussed.

Table II shows the distribution of fetuses by weight and sex according to presence or absence of the centers, as indicated by the plus and minus symbols. The  $\pm$  symbol indicated doubt as to whether the center was present or not. It is seen that average weight increased with the number of centers present, and, on the average, female infants weighed less than male infants in the same group.

TABLE II. PRESENCE OR ABSENCE OF DISTAL EPIPHYSIS OF FEMUR AND PROXIMAL EPIPHYSIS OF TIBIA IN RELATION TO ESTIMATED WEIGHT AND SEX OF FETUS

ESTIMATED WEIGHT AT TIME OF ROENTGENOGRAM* (GRAMS)	FEMUR - TIBIA -		FEMUR $\pm$ TIBIA -		FEMUR + TIBIA -		FEMUR + TIBIA $\pm$		FEMUR + TIBIA $\pm$	
	M	F	M	F	M	F	M	F	M	F
Under 1,000	3									
1,000-1,499		1								
1,500-1,999	4	2				4				1
2,000-2,499	5			2	3	6		1		1
2,500-2,999	2		1	1	5	5	1	2	3	3
3,000-3,499	1		1		7	4	5	1	4	3
3,500-3,999						2	1	1	6	3
4,000 and over		1			1				1	
Total	15	4	2	3	16	21	7	5	14	16
Average Weight	2,000	2,350	2,980	2,480	2,980	2,600	3,260	3,030	3,530	3,450

\*Estimated from birth weight.

In the group with neither center present, the fetuses were, with two exceptions, immature or just barely mature at the time of the roentgenogram. The two males in the weight group 2,500 to 3,000 grams weighed about 2,600 and 2,700 grams; one was born a day later and was said to be immature; the other had only thirty-four weeks of gestation and was born forty days later. These are probably borderline cases. The other two fetuses were mature; they weighed 3,400 to 4,600 grams and were said to be mature when born four days after the roentgenogram. Either the centers of ossification were not present, or else were present but did not show on the roentgenogram. The error which would have been made in judging all of these fetuses immature on the basis of the roentgenogram alone is about two out of twenty cases, or 10 per cent.

At the other extreme, all the fetuses with both centers present weighed over 2,500 grams with the exception of two females. The one weighing between 1,500 and 2,000 grams was born fourteen days later, at which time it weighed 2,040 grams and was said to be a mature but very scrawny baby. The other probably weighed about 2,400 grams at the time of the roentgenogram, and was born thirty-two days later. Since both the infants were girls, they were probably not quite as immature as their weight would indicate.

Looking next at the group with the epiphysis of the femur present and the epiphysis of the tibia absent, we see that thirteen, or about one-third, weighed under 2,500 grams. Ten of the thirteen were females and five of the ten were twins or triplets; seven of the thirteen weighed over 2,250 grams, all of which would indicate that perhaps half of these thirteen were bordering on maturity. This would mean that about 20 per cent of the fetuses with only one of the centers present were definitely immature. The four infants weighing under 2,000 grams were females, and two were from a set of triplets. Thus, on the basis of presence or absence of the centers alone, fetuses in this group would be judged "probably mature," but there would be a higher proportion of errors than in the groups with both centers either present or absent.

The small group with the epiphysis of the femur doubtful and the tibia not present were about evenly divided on either side of the 2,500 gram line. The group with the epiphysis of the femur present and the epiphysis of the tibia



doubtful weighed over 2,500 grams except for one case, a female who weighed 2,440 grams and was born four days later and said to be "early."

Thus, if one were to judge maturity of the fetus in utero solely from the presence or absence of these two centers, one would have made an appreciable error in about 10 per cent of the cases where both centers were either present or absent, and in about 20 per cent of the cases where only the distal femoral epiphysis was present. It would be desirable to have a measure of the risk of death from immaturity should delivery occur in these cases, but several hundred observations on babies delivered shortly after the roentgenograms would be needed before these risks could be determined. There was only one death attributed to immaturity among the infants in this study. This was a girl weighing 2,400 grams at birth and for whom the presence of the distal femoral epiphysis was doubtful, the proximal tibial epiphysis being absent, on roentgenogram taken seven days before birth. The relation between presence or absence of the centers and each of the other two criteria of maturity studied, estimated length and period of gestation, was quite similar to that for weight and will not be discussed.

RELATION BETWEEN WEIGHT OF FETUS AS ESTIMATED FROM X-RAY AND  
WEIGHT AT TIME OF X-RAY AS ESTIMATED FROM BIRTH WEIGHT  
(INFANTS BORN 7 DAYS OR LESS AFTER X-RAY, 50 CASES)

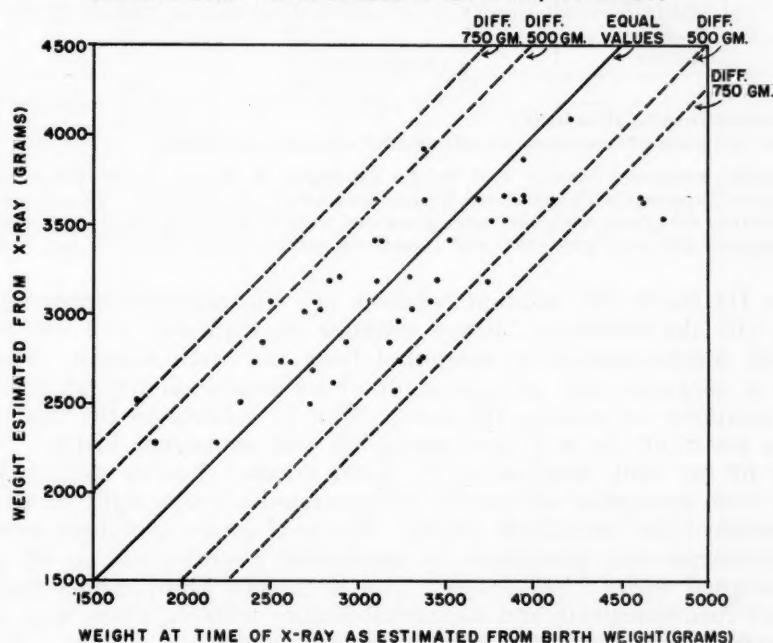


Fig. 1.

Turning now to the quantitative estimates of weight and gestation made from the roentgenogram, we have in Fig. 1 the relation between weight as estimated from the roentgenogram and weight of the fetus as estimated from the birth weight. The estimate based on birth weight is shown on the horizontal scale and the estimate made from the roentgenogram is shown on the vertical axis. Each case is represented by a dot opposite the appropriate values on the two scales. Fig. 1 includes only babies born within a week of the roentgenogram so that the birth-weight estimate (on the horizontal scale) is reasonably accurate. Cases in which the roentgenogram estimate agreed exactly with the birth-weight

estimate would lie on the solid diagonal line. The first two dotted lines on either side of the solid line represent differences of 500 grams in either direction. Thirty-eight out of fifty, or 75 per cent, of the cases lie between these two dotted lines, and for these cases the roentgenogram estimate differs by less than 500 grams from the birth-weight estimate. The outside dotted lines represent differences of 750 grams. Forty-six cases, or 92 per cent, fall within these limits. On the average, the roentgenogram estimates fell below about as often as they exceeded the actual weight except in the group of large infants weighing over 4,500 grams where the roentgenogram estimates were consistently too low. The same relationship existed when all cases were included. The proportion of total cases for which the two estimates of weight were within 500 grams or 750 grams of each other was about the same as for infants born within a week of roentgenogram. There were a few more cases where the differences were quite large.

TABLE III. COMPARISON OF MATURITY AS ESTIMATED BY ROENTGENOGRAM, MATURITY ACCORDING TO MENSTRUAL HISTORY, AND WEIGHT AS ESTIMATED FROM BIRTH WEIGHT

MATURITY		WEIGHT IN GRAMS*		TOTAL CASES	PER CENT UNDER 2,500 GRAMS
ROENTGENO- GRAM†	MENSTRUAL HISTORY	UNDER 2,500	2,500 AND OVER		
Premature	Premature	16	10	26	62%
Premature	Mature	8	4	12	67%
Mature	Premature	8	9	15	40%
Mature	Mature	3	44	47	6%
Total		33	67	100	33%

\*Estimated from birth weight

†Based on week of gestation as estimated from roentgenogram.

Roentgenogram, menstrual history, and weight all agree in 60/100 or 60 per cent of cases. Roentgenogram disagrees with menstrual history and weight in 10/100 or 10 per cent of cases. Menstrual history disagrees with roentgenogram and weight in 17/100 or 17 per cent of cases. Weight disagrees with roentgenogram and menstrual history in 13/100 or 13 per cent of cases.

Table III shows the relation between (a) the roentgenogram estimate of maturity, (b) the menstrual-history estimate of maturity, and (c) weight at the time of roentgenogram as computed from the birth weight. These three measures of maturity are, of course, obtained independently of one another. Data are available on exactly 100 cases. The 26 infants on the first line were premature according to both roentgenogram and menstrual history. Of these 26, 16, or 62 per cent, weighed under 2,500 grams. Twelve were judged premature by roentgenogram but mature by menstrual history; eight, or 67 per cent, of these weighed less than 2,500 grams. The next group of fifteen were mature by roentgenogram but premature by menstrual history; six, or 40 per cent, of these weighed under 2,500 grams. And in the last group which were mature by both the roentgenogram and menstrual-history criteria, there were three out of forty-seven, or 6 per cent, who weighed under 2,500 grams. Among the cases studied, the results from the roentgenograms appear to agree slightly better with weight than data from menstrual history. Another way of stating the results is that all three criteria of maturity agreed in 16 plus 44, or 60 per cent, of the cases. Roentgenograms disagreed with the other two criteria in 4 plus 6, or 10 per cent, of the cases, and menstrual history disagreed with the two other criteria in 8 plus 9, or 17 per cent, of the cases. Weight disagreed with the other criteria in 10 plus 3, or 13 per cent, of the cases.

### Summary and Conclusions

1. The present study is regarded as preliminary in nature and was designed to determine whether estimates of maturity of the fetus in utero could be made with reasonable accuracy.

2. A technique for visualizing fetal parts was developed and the long bones of 100 fetuses in utero were studied for osseous development. This was related to estimated weight at the time the roentgenogram was taken.

3. The study revealed that average weight of the fetus increases with the number of centers present.

4. It was judged by this study that if maturity of the fetus were determined solely from the presence or absence of the centers for the distal femur and proximal tibia one would make an appreciable error in about 10 per cent of the cases when both centers were either present or absent; and in about 20 per cent of the cases when only the distal femoral epiphysis was present.

5. In 76 per cent of the cases studied the roentgenogram estimate of weight differed by less than 500 grams from the actual birth-weight estimate and in 92 per cent of the cases studied the difference fell within 750 grams.

6. On the basis of the results obtained, it is believed that the method shows promise, and that it very likely could be improved with further study. On the other hand, it can be expected that there will be a certain proportion of failures which are due either to imperfections in the roentgenograms or to individual variability in the development of centers of ossification.

#### References

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## THE ETIOLOGICAL SIGNIFICANCE OF ERGOT IN THE INCIDENCE OF POSTPARTUM NECROSIS OF THE ANTERIOR PITUITARY\*

### A Preliminary Report

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POSTPARTUM necrosis of the anterior portion of the pituitary gland has been frequently associated with postpartum hemorrhage and obstetric shock. Sheehan<sup>1</sup> described thrombosis of the pituitary vessels as a possible factor. Sheehan and Murdoch,<sup>2</sup> in a presentation of the pathologic and clinical aspects of the pituitary deficiency syndrome, have pointed out that the condition was not found in those who were injured during the war and who later died of acute, severe blood loss. They called attention to the puerperal involution of the hypertrophied anterior pituitary of pregnancy and the vascular changes favoring and ultimately causing thrombosis of the pituitary vessels. The purpose of this paper is to point out the possible relation of ergot to postpartum necrosis of the anterior pituitary.

The history is presented of a woman who developed the signs and symptoms of hypopituitarism following a delivery associated with hemorrhage and shock. She received ergot in the management of the third stage of labor and during the immediate puerperium, with the development of transient signs of ergotism.

### Case Report

CASE No. 43897.—HISTORY.—A 26-year-old married woman was admitted to the American University Hospital of Beirut, Lebanon, on June 5, 1947, 79 days following her last delivery, for general weakness, amenorrhea, polydipsia and polyuria of approximately two months' duration.

The past medical history revealed three previous full-term normal deliveries. The patient was readmitted after her last delivery (November, 1945) in a state of shock with severe, delayed postpartum hemorrhage. She was immediately given 500 Gm. of dried plasma followed by 500 c.c. of whole blood intravenously, as well as ergot and Pituitrin, hypodermically. A dilatation and curettage were performed and some retained placental tissue was removed. During the patient's eight-day hospital stay, she received 26 doses of ergot, each of 0.2 mg. (Ernutin, Burroughs Wellcome & Co., Inc.) hypodermically, and 15 units of obstetrical Pituitrin. She recovered and was discharged.

The patient was readmitted to the Obstetrical Service on March 17, 1947, with a twin pregnancy of 38 weeks' gestation. The membranes had spontaneously ruptured prematurely and the patient was not in labor. Urinalysis was normal and blood pressure was 118/70 with no signs or symptoms of toxemia. The patient developed an intrapartum

\*Presented by Dr. Nassar, by invitation, before the Richmond Obstetrical and Gynecological Society, Sept. 24, 1948, in Richmond, Va.



infection, with chills and fever, and, soon thereafter, went into labor. Following the delivery of stillborn twins, the placenta was retained and there was free bleeding for which  $2\frac{1}{2}$  units of Pituitrin were given intravenously. The bleeding diminished appreciably, but the patient went into shock. The radial pulse could not be felt, blood pressure was not obtainable, and the patient was covered with clammy perspiration. Eighteen hundred c.c. of 5 per cent glucose in saline and 1,000 c.c. of whole blood were given intravenously. The patient's condition improved and the placenta was manually removed two hours following the delivery. She was given 10 units of Pituitrin and 0.2 mg. of ergot, hypodermically, after the extraction of the placenta. The postpartum course was stormy. She was put on penicillin injections every two hours, each 50,000 units, and Ergotrate tablets orally, each 1.0 mg., three times daily for nine doses.

On the fourth postpartum day, following the last dose of Ergotrate, the blood pressure could not be obtained in either arm, and the radial pulsations could not be palpated. The pulsations of the dorsalis pedis vessels could be felt. The patient developed cold extremities and acrocyanosis, more marked in the hands than in the feet. A diagnosis of "ergotism" was made. The patient was given repeated small blood transfusions (total 950 c.c.), injections of, suprarenal cortical extract, vitamins B and C, and 5 per cent glucose in saline, intravenously, during the postpartum period. It is interesting to note that, in spite of the omission of estrogenic preparations, the breasts remained dry throughout the puerperium. The patient was dismissed in apparent good health and with normal peripheral circulation on the seventeenth postpartum day.

*Present Illness.*—Shortly after being discharged from the hospital, the patient began to experience excessive thirst, drinking thirty to thirty-five glasses of water daily and having to get up to void five or six times during the night. She also reported a sensation of generalized weakness, frequent sore throat, and headache.

*Physical Examination.*—Examination 79 days after delivery revealed atrophic breasts, hyperpigmented areolae and normally involuted pelvic organs. Blood pressure was 90/50. The urine was clear, of a watery appearance, with a specific gravity of 1.003 and no abnormal findings. Basal metabolic rate was -22 per cent, blood cholesterol, 250 mg. per cent, and the patient was unable to concentrate the urine above 1.014. Skull film revealed a normal sella turcica and no suprasellar calcification. The visual fields were within normal limits. The fluid intake and output, in the hospital, varied between 4,900 and 5,000 c.c. in 24 hours. A diagnosis of diabetes insipidus with possible postpartum hypopituitarism was made. The patient was discharged on 5 units of Pituitrin, hypodermically, twice daily.

*Follow-Up.*—Oct. 6, 1947, six months postpartum: The patient had taken the treatment as prescribed, with much relief. On one occasion the treatment was interrupted for five days with a total recurrence of symptoms. She also reported the following new developments: falling of scalp, axillary, and suprapubic hair, loss of appetite and libido, episodes of conjunctival irritation and lachrimation, increased sensitiveness to cold, diminution in size of the breasts, general weakness with easy fatigability, frequent headache, and the persistence of amenorrhea. Examination revealed that the scalp, axillary, and suprapubic hair was markedly diminished, the breasts atrophic, nipples and areolae hyperpigmented, and the uterus definitely hyperinvoluted. Glucose tolerance curve was flattened with a fasting level of 58 mg. per cent. The patient was advised to continue the same treatment with the addition of 1 grain of thyroid extract, twice daily.

Nov. 10, 1947, eight months postpartum: The patient had taken the Pituitrin therapy as prescribed. She took the thyroid pills only for a few days and discontinued them because of intolerance. She reported some improvement in appetite and the sensation of hot flashes over the chest, neck, and face, about three times a week. The other signs and symptoms remained unaltered. She was asked to discontinue Pituitrin therapy and was prescribed hematinics and vitamin B.

April 5, 1948, fourteen months following delivery: The patient reported that she was slightly more uncomfortable since discontinuing therapy, but more comfortable than

at the time of onset of polydipsia and polyuria. She reported no other change in the signs and symptoms from the time of her previous visit. On examination, the findings were essentially the same as described at the previous examination.

June 11, 1948, sixteen months following delivery: The patient reported a sensation of fullness in the breasts. She also felt severe, bilateral groin pain, of a lancinating and cramplike nature, that started on May 13, and persisted for three days. On May 26, the same pain recurred with more severity and was localized in the right groin. The following day, the patient bled from the vagina for the first time in sixteen months, changing three to four pads every twelve hours for the first twenty-four hours, then the bleeding became spotting in nature and persisted through May 31. The blood was bright red and did not contain clots. The patient, however, continued to complain of the previous signs and symptoms. On examination, there was no evidence of increased mammary gland structure. The suprapubic and axillary hair remained scant, the nipples and areolae hyperpigmented, and the pelvic organs approached normal size. Blood pressure rose to 116/70, weight remained at 100 pounds, blood cholesterol was 200 mg. per cent, and blood sugar, 68 mg. per cent.

Simmonds' Disease was first described by Simmonds in 1914. Cachexia is so often associated with the severe cases of this disease that the syndrome has been erroneously called, "pituitary cachexia." The underlying pathology of this condition is a variable degree of destruction of the anterior pituitary from one cause or another. There may exist milder cases of Simmonds' disease where the only clinical manifestation of hypopituitary function is amenorrhea or deranged pituitary-ovarian function. There are cases of diabetes insipidus reported in the Year Book of Endocrinology, Metabolism, and Nutrition, 1946, associated with Simmonds' disease.

It was suggested by Dr. Harold Teel that, since this patient developed Simmonds' disease following postpartum hemorrhage and ergotism, and also, since this condition is not encountered in individuals who have recovered from massive hemorrhage from other causes, there may be a causal relationship between the administration of ergot to exsanguinated patients and the development of Simmonds' disease.

### Experimental

The white rat was chosen for the subject of experiment. There has been little work reported in the literature on the effects and dosage of ergot in white rats; however, some reports classify rats among the ergot-resistant group of animals. It was found, however, that the administration of 7.2 mg. of ergotoxine ethanesulfonate intraperitoneally to rats weighing 50 grams was lethal to them in three hours. Ergotoxine ethanesulfonate was used in this experiment because it was the only powder form of ergot available that could be dissolved in the required high concentration necessary to administer it effectively in small bulk. The rats were divided into groups as follows:

*Group 1.*—Fifteen rats were bled by cardiac puncture of 1.4 to 3.0 per cent of their total body weight. That amount of blood represents a sizeable proportion of the animal's total blood volume. Carrying the analogy over to the human being, 2 per cent of the total body weight, in blood, of an individual weighing some 70 kilograms, is 1,400 c.c. of blood, which is approximately one-fourth of this individual's total blood volume. These animals were allowed to go into a state of shock and were then sacrificed two to ten days later. The pituitary, adrenal, and thyroid glands were removed and fixed in formalin. The criteria for shock were listlessness, lying immobile on the back, lack of response to stimuli, and inability to resume and maintain the upright position.

*Group 2.*—This group included twenty-one rats. They were bled by cardiac puncture of 1.1 to 3.1 per cent of their total body weight and were then given from 0.35 to 4.0 mg.

Fig. 1.

Fig. 2.

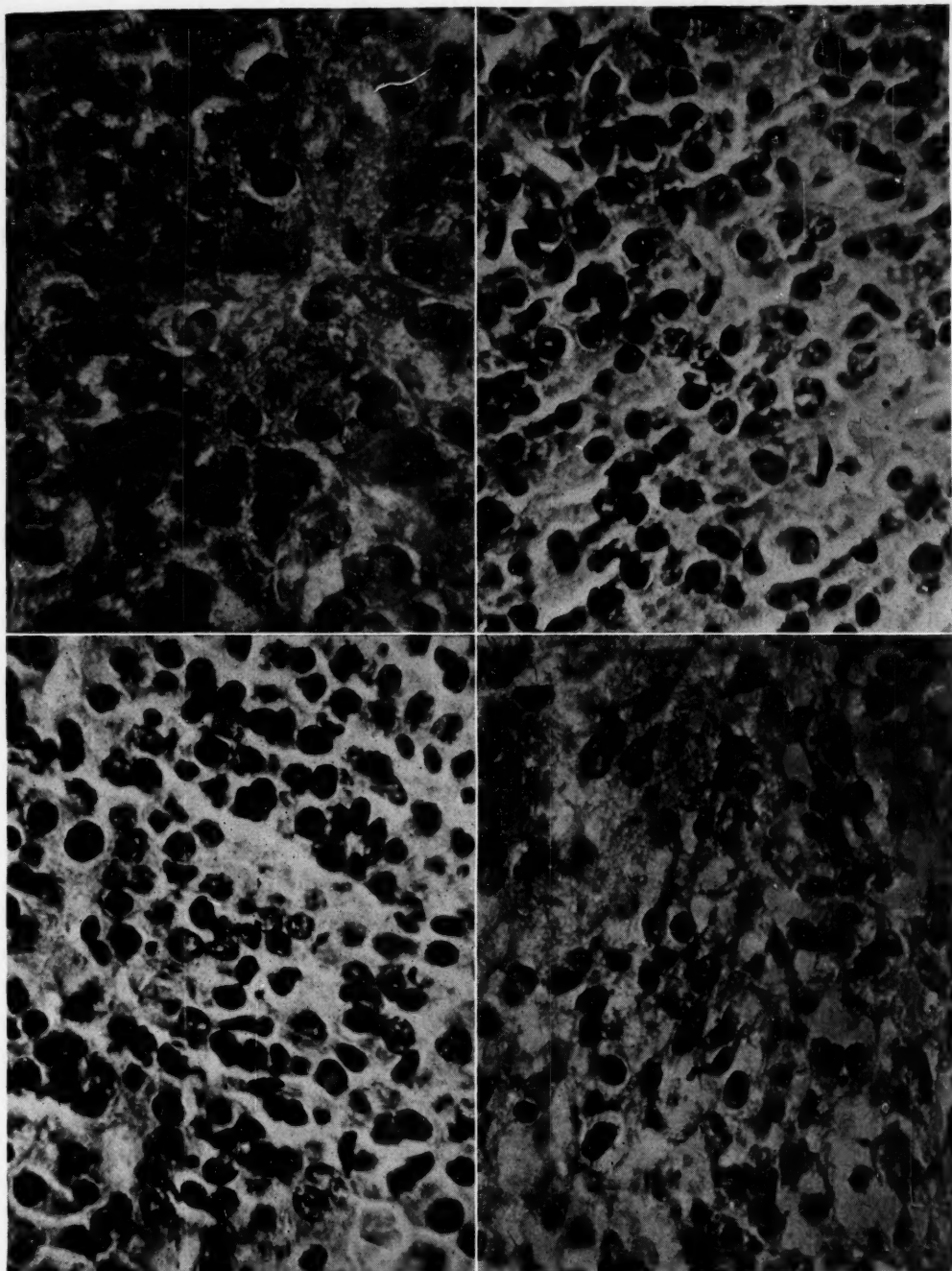


Fig. 3.

Fig. 4.

Fig. 1.—Normal anterior pituitary of the white rat. The distinct nuclei and nucleoli and the granular character of the nuclei are evidence of healthy cells.

Fig. 2.—There is an increased proportion of pyknotic nuclei. The fragmentation of the nuclear material and nuclear limiting membrane of the cells in the center of the field is evidence of damage probably resulting from ergot and hemorrhage.

Fig. 3.—The increased proportion of pyknotic nuclei and the peripheral location of the nuclei in some of the cells, and, also, a few cells showing disrupted nuclear membranes are positive evidence of tissue destruction.

Fig. 4.—There is an abundance of pyknotic nuclei and the large areas of cytoplasmic collections with total absence of nuclei indicates cellular destruction.



of ergotamine ethanesulfonate, intraperitoneally, per 50 grams of body weight. These animals were sacrificed at periods varying from six hours to twenty-six days.

*Group 3.*—Twenty-one rats which were not bled were given from 1.6 to 6.6 mg. of ergotamine ethanesulfonate, intraperitoneally, per 50 grams of body weight. These animals were also sacrificed at periods varying from six hours to twenty-six days.

*Group 4.*—The control group included six animals. These rats were given from 0.5 to 3.2 c.c. of the solvent used to dissolve the ergotamine ethanesulfonate, intraperitoneally, per 50 grams of body weight.

Serial paraffin sections were made of the pituitary, adrenal, and thyroid glands. Alternate sections were stained by hematoxylin-eosin and the Mallory method.

The results of the histological examination are briefly summarized as follows:

*Group 1.*—The pituitary, thyroid, and adrenal glands of the fifteen rats in this group were normal, except the anterior lobe of one pituitary which showed signs of congestion.

*Group 2.*—The anterior lobes of all the twenty-one rats in this group showed foci of necrosis, but the other parts of the pituitary were essentially normal. The adrenals and thyroids were also normal. The foci of necrosis were characterized by nuclear pyknosis, and karyorrhexis, and well-defined aggregations of cytoplasm were observed with a total absence of nuclei (Fig. 2 to 4).

*Group 3.*—The anterior lobes of the pituitaries of the twenty-one rats in this group all showed areas of necrosis. The anterior lobe of one gland was totally destroyed. In one animal there were signs of atrophy of the thyroid-secreting cells and absorption of colloid material. The adrenal cortex of the same animal had focal areas of congestion and necrosis with cloudy degeneration. The adrenals and thyroids of the other rats showed no pathological changes.

*Group 4.*—The six control rats had no abnormal pathological condition in the pituitary, adrenal, or thyroid glands (Fig. 1).

### Comment and Conclusions

The writers believe that the results of this preliminary experiment seem to indicate a possible etiological relationship between the administration of ergot alkaloids to exsanguinated patients and the incidence of postpartum destruction of the anterior portion of the pituitary. This paper is a preliminary report and it is hoped that in the future more accurately controlled experiments will be performed using others of the ergot alkaloids. Several interesting points, which may be worthy of consideration, have emerged as a result of this experiment:

1. To what extent can this technique be developed as a valid means to assist pituitary physiologists in determining the function or functions of the anterior lobe of the pituitary gland, without having to resort to total or partial gland ablation?

2. Are the changes noticed in the thyroid and adrenal glands in the above study true, direct effects of ergot on these glands, or are they secondary effects following destruction of the anterior pituitary?

The writers wish to thank Dr. Harold Teel, former Professor of Obstetrics and Gynecology at the Medical School of the American University of Beirut, Lebanon, for suggesting the problem; Dr. James Butcher, formerly of the Department of Surgical



Pathology of the Medical College of Virginia, for his help with the interpretation of the histological sections; and Dr. William Bickers, of the Department of Gynecology of the Medical College of Virginia, for his assistance in the preparation of the paper for publication. This investigation was aided by a grant to Dr. William Shanklin from the Committee for Research in Endocrinology, National Research Council.

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## THERAPEUTIC ABORTIONS IN NEW YORK CITY, 1943-1947\*

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VERY few statistical studies of therapeutic abortion have been made in the United States. A search of the literature of the last decade produced only four papers,<sup>3, 5, 8, 9</sup> covering about 700 cases extending over more than twenty years. This sample is too small for the computation of a valid fatality ratio and too highly selected to permit an evaluation of the practices prevailing among the medical profession at large. It appears worth while, therefore, to supplement the clinical data by a report on almost 3,600 therapeutic abortions based upon the registration† of fetal deaths in New York City during the five-year period from 1943 through 1947.

### Material

From the published volumes of vital statistics for the City of New York<sup>7</sup> the number of registered fetal deaths associated with the operative procedures commonly employed in therapeutic abortion can be compiled to be 3,660 in 1943-1947. The current series consists of only 3,592 cases, due to the exclusion of 50 viable infants and other errors. Of these 3,592 interruptions, 1,525 were performed in proprietary hospitals, 1,951 or more than half in voluntary hospitals, and 112 in municipal hospitals. Four abortions were registered as having taken place "at home," but it appears more likely that they were done in the doctor's office. Most of the women concerned were private patients, only one-eighth having been treated on general service.

During the years 1943-1947 more than 710,000 live births and about 57,000 fetal deaths were registered in New York City. The 3,592 therapeutic abortions, therefore, corresponded to ratios of 5.1 per thousand live births and 4.7 per thousand known pregnancies. One is inclined to assume that reputable physicians performing such operations will make sure to comply with all legal requirements, but this may not always be the case. Some doctors may not even know that in New York City every fetal death has to be registered regardless of the period of gestation. The degree of completeness achieved in the registration of therapeutic abortions cannot be estimated from the available data.

The incidence of therapeutic abortions in New York City, as computed from this series, is on the same order of magnitude as in Sweden<sup>10</sup> and Denmark,<sup>1, 4</sup> where reporting has long been mandatory and is believed to be reasonably complete. In Sweden, 1939-1945, the ratio was 4.6 per thousand live births and in Denmark, 1932-1940, it was 6.0 against 5.1 in New York City. In Germany, 1936-1940, it was only 1.4 per thousand live births,<sup>2, 6</sup> but this was the result of the strictest supervision by a totalitarian government dedicated to an expansionist population policy. None of these ratios includes abortions for eugenic reasons and other types of indications recognized in some foreign countries but not in the United States.

\*Read, by invitation, before the New York Obstetrical Society, on Dec. 13, 1949.

†The author is greatly indebted to Mr. Carl L. Erhardt and his associates at the Bureau of Records and Statistics of the Department of Health for making this material accessible and for the generous cooperation extended to him throughout the investigation.

The numbers of therapeutic abortions registered in New York City and the ratios per thousand known pregnancies varied moderately from year to year (Table I), but there was no clear trend either up or down.

Of the women undergoing therapeutic abortion, 3,046 were residents of New York City and 544 were known to be nonresidents (Table I). The home of two mothers was not stated. The percentage of nonresidents was 15.2 against 3.9 among all women terminating a pregnancy in 1943-1947.

TABLE I. THERAPEUTIC ABORTIONS BY YEAR OF REGISTRATION, RESIDENCE, COLOR, AND AGE OF MOTHER

	NUMBER OF CASES	RATIO PER THOUSAND KNOWN PREGNANCIES
1943	680	4.7
1944	689	5.2
1945	687	4.9
1946	803	4.8
1947	733	4.0
New York City	3,046	4.1
Nonresident	544	18.4
Not stated	2	-
Manhattan	1,089	7.2
Bronx	619	4.4
Brooklyn	820	2.9
Queens	491	3.4
Richmond	27	1.5
White	3,445	5.0
Other races	147	2.0
Under 20 years	71	2.0
20-24 years	374	2.0
25-29 years	742	3.0
30-34 years	968	5.2
35-39 years	938	10.7
40-44 years	431	24.5
45 years and over	54	51.6
Not stated	14	-
Total	3592	4.7

The ratios of therapeutic abortions per thousand known pregnancies were sharply different in the five boroughs: highest in Manhattan, near the average in the Bronx, Queens, and Brooklyn, and lowest in Richmond (Table I). These figures are tabulated by residence of mother, not by place of operation. All differences are statistically significant. They suggest that economic and cultural factors play a considerable role in determining the incidence of therapeutic abortion. It is possible, however, that they merely reflect differences in completeness of registration.

The great majority of the 3,592 women were white. Only 147, or 4.1 per cent, belonged to other races, most of them Negroes (Table I). The ratio per thousand known pregnancies was 5.0 for the white and 2.0 for the colored population. The low ratio for nonwhites is partially explained by the fact that pregnant colored women in New York City were on the average 3.4 years younger than white women. Standardized for age, the ratios of therapeutic abortions per thousand known pregnancies were 4.9 and 2.9 for white and colored. It may be pointed out that the majority of the nonwhite population of New York City lives in Manhattan, where the recorded incidence of therapeutic abortions was highest.

The average age of all women in this series was 33 years. About one-eighth of them were below 25 and a slightly larger number in their forties. The ratio

of therapeutic abortions per thousand known pregnancies increased rapidly with age, especially after the third decade of life (Table I). The ratio was twenty-five times higher among the oldest than among the youngest women. Information on marital status is unfortunately not available.

In 1,110, or 30.9 per cent, of all cases the interrupted pregnancy had been the first. The remainder was divided about evenly among second, third, and later pregnancies (Table II). The average number of previous pregnancies was 2.3 for the plurigravidas and 1.6 for all women in the series.

TABLE II. THERAPEUTIC ABORTIONS BY ORDER OF PREGNANCY AND BY PERIOD OF GESTATION

	CASES	PER CENT
First	1,110	30.9
Second	825	23.0
Third	853	23.8
Fourth	400	11.1
Fifth	198	5.5
Sixth	90	2.5
Seventh	55	1.5
Eighth	22	0.6
Ninth	19	0.5
Tenth and later	19	0.5
Not stated	1	-
1-4 weeks	141	4.0
5-8 weeks	1,936	54.9
9-12 weeks	949	26.9
13-16 weeks	300	8.5
17-20 weeks	140	4.0
21-24 weeks	39	1.1
25-28 weeks	24	0.7
Not stated	63	-
Total	3,592	100.0

Period of gestation is conventionally stated in terms of weeks elapsed since the onset of the last menstrual period, but some physicians apparently preferred to reckon from the estimated time of conception. The great majority of interruptions were performed in the first trimester of pregnancy and only very few after the twentieth week (Table II). This pattern did not vary significantly from year to year. In 63 cases the period of gestation was not recorded.

TABLE III. THERAPEUTIC ABORTIONS BY PERIOD OF GESTATION AND TYPE OF CARE\*

WEEKS OF GESTATION	PROPRIETARY HOSPITALS	OTHER HOSPITALS PRIVATE SERVICE	OTHER HOSPITALS GENERAL SERVICE
<i>Cases.—</i>			
1-8	978	988	108
9-12	383	403	157
13-16	85	124	90
17-28	40	101	61
Total	1,486	1,616	416
<i>Per Cent.—</i>			
1-8	65.8	61.1	26.0
9-12	25.8	24.9	37.7
13-16	5.7	7.7	21.6
17-28	2.7	6.2	14.7
Total	100.0	100.0	100.0

\*Excluding 74 cases with period of gestation or type of care not stated.

Women treated on the general wards of voluntary and municipal hospitals tended to be further advanced in their pregnancies than private patients in the same types of hospitals. Operations in proprietary hospitals were performed



still earlier (Table III). The differences between the three groups of cases are statistically highly significant and not likely to be affected by incomplete registration. The higher percentages of comparatively late therapeutic abortions among ward patients may be the results of inadequate prenatal care or else of stricter standards of indication than were applied on the private service.

A great variety of complications of pregnancy were reported as indications for the therapeutic abortions in this series. They are summarized in Table IV. This tabulation had to be made in terms of the 1939 revision of the International List of Causes of Death which is not ideally suited for the purpose. The most frequent indications were heart disease, nonmalignant tumors of the uterus, mental disorder, the toxemias of pregnancy including renal and hypertensive disease, and tuberculosis. Each of these was listed in more than 10 per cent of all cases and together they accounted for two-thirds of the whole series.

TABLE IV. THERAPEUTIC ABORTIONS BY COMPLICATION OF PREGNANCY

		NUMBER OF CASES	PER CENT OF CASES
Cardiac		622	17.3
Fibroids (Nonmalignant tumors of uterus)		512	14.3
Mental		471	13.1
Schizophrenia	73		
Manic-depressive psychosis	182		
Other (mostly psychoneuroses)	216		
Toxemia including renal & hypertensive disease		446	12.4
Hyperemesis	96		
Nephritis	134		
Hypertension	93		
Other and unspecified	123		
Tuberculosis		376	10.5
Pulmonary	351		
Other	25		
Endocrine		147	4.1
Exophthalmic goiter	89		
Diabetes mellitus	46		
Other	12		
Nervous		106	3.0
Epilepsy	49		
Disseminated sclerosis	29		
Other	28		
Hemorrhage		98	2.7
Other		814	22.7
Pyelitis	60		
Breast cancer	35		
Other malignant tumors	22		
Asthma	26		
Miscellaneous	446		
Not reported	225		
Grand total		3,592	100.0

Therapeutic abortions associated with mental disorder increased steadily from 1943 to 1947. The numbers of cases so registered in each year were 56, 74, 78, 123, and 140, corresponding to 8.2, 10.7, 11.4, 15.3, and 19.1 per cent of all abortions. The ratio per thousand known pregnancies was 0.4 in the first and 0.8 in the last year of the series. No consistent trend was apparent for any other major type of indication. It is of some interest that among the miscellaneous complications were seven cases of German measles, all registered in 1946 and 1947.

Table V presents the distribution of therapeutic abortions by complication of pregnancy and age of mother. As shown in the middle panel, fibroids in-

creased from less than 2 per cent among the youngest to 30 per cent among the oldest patients, whereas for all other indications the percentages either declined or did not change significantly. However, the ratio per thousand known pregnancies increased with age for every indication, but more steeply for some than for others.

TABLE V. THERAPEUTIC ABORTIONS BY COMPLICATION OF PREGNANCY AND AGE OF MOTHER\*

	UNDER 25 YEARS	25-29 YEARS	30-34 YEARS	35-39 YEARS	40 YEARS AND OVER
<i>Number of Cases.—</i>					
Cardiac	99	134	165	153	69
Fibroids	7	37	124	197	146
Mental	82	110	128	115	36
Toxemia, etc.	57	98	111	111	64
Tuberculosis	67	114	109	54	31
Endocrine	20	26	42	36	23
Nervous	21	22	25	27	11
Hemorrhage	15	16	28	21	18
Other	77	185	236	224	87
Total	445	742	968	938	485
<i>Per Cent of Cases.—</i>					
Cardiac	22.2	18.1	17.0	16.3	14.2
Fibroids	1.6	5.0	12.8	21.0	30.1
Mental	18.4	14.8	13.2	12.3	7.4
Toxemia, etc.	12.8	13.2	11.5	11.8	13.2
Tuberculosis	15.1	15.4	11.3	5.8	6.4
Endocrine	4.5	3.5	4.3	3.8	4.7
Nervous	4.7	3.0	2.6	2.9	2.3
Hemorrhage	3.4	2.2	2.9	2.2	3.7
Other	17.3	24.9	24.4	23.9	17.9
Total	100.0	100.0	100.0	100.0	100.0
<i>Per 1,000 Known Pregnancies.—</i>					
Cardiac	0.4	0.5	0.9	1.7	3.7
Fibroids	0.0	0.1	0.7	2.2	7.8
Mental	0.4	0.4	0.7	1.3	1.9
Toxemia, etc.	0.3	0.4	0.6	1.3	3.4
Tuberculosis	0.3	0.5	0.6	0.6	1.7
Endocrine	0.1	0.1	0.2	0.4	1.2
Nervous	0.1	0.1	0.1	0.3	0.6
Hemorrhage	0.1	0.1	0.2	0.2	1.0
Other	0.3	0.7	1.3	2.5	4.7
Total	2.0	3.0	5.2	10.7	26.0

\*Excluding 14 mothers of unstated age.

The median duration of pregnancy for all cases was 7.4 weeks. Tabulated by complication it varied from 6.8 to 8.1 weeks, except for hemorrhage, where it was 12.2 weeks. This statistically significant difference reflects the vital nature of the indication, which may constitute a most serious obstetric emergency. In this connection it should be mentioned that in about one-half of the pregnancies interrupted after the twentieth week prior death of the fetus was reported. The propriety of including these types of cases as well as some of the pregnancies complicated by fibroids in a series of therapeutic abortions is of course open to question.

Of the 3,592 therapeutic abortions, 2,703, or about three-fourths, were accomplished by dilatation and curettage, 534 by hysterectomy, and 294 by hysterotomy. In 61 cases the type of operation was not recorded. The choice of operation seems to have been determined primarily by the nature of the condition complicating pregnancy and by the period of gestation. The close association between nonmalignant tumors of the uterus and hysterectomy is apparent in Table VI. Of the 512 pregnancies complicated by fibroids, 398, or

almost four-fifths, were terminated by hysterectomy. Conversely, three-fourths of the hysterectomies involved fibroids. Of abortions for reasons other than fibroids, 87.0 per cent were accomplished by dilatation and curettage. This was the method chosen for 95.8 per cent of interruptions not involving fibroids and performed during the first eight weeks of pregnancy, but with increasing duration the vaginal approach lost ground to hysterotomy and hysterectomy.

TABLE VI. THERAPEUTIC ABORTIONS BY COMPLICATION OF PREGNANCY AND TYPE OF OPERATION

	DILATATION AND CURETTAGE	HYSTERECTOMY	HYSTEROTOMY	NOT STATED
Cardiac	555	13	40	14
Fibroids	76	398	37	1
Mental	429	6	31	5
Toxemia, etc.	374	15	46	11
Tuberculosis	333	10	23	10
Endocrine	128	7	6	6
Nervous	91	3	12	-
Hemorrhage	35	32	29	2
Other	682	50	70	12
Total	2,703	534	294	61

To study mortality connected with therapeutic abortion, the names and addresses of the 3,592 women were checked against the files of deceased persons for the same and the next two years. Women undergoing therapeutic abortion in 1947 were followed through 1948 only. The search produced 50 deaths of residents of New York City occurring within two years after the operation, corresponding to an annual mortality rate of 9.1 per thousand. Coverage achieved by this method is believed to be complete for the period immediately after the operation but less satisfactory for later months due to changes of residence or of marital status. The death rate of 9.1 per thousand is therefore a minimum value. As computed it indicates a mortality three times as heavy as that prevailing among the general population of New York City, taking age and color into consideration.

Of the 50 deaths (Table VII), seven should apparently be ascribed to the operation. The cause of death was given as shock in two cases, as pulmonary embolism three times, once as ileus, and once as meningococcus meningitis and pneumonia. This patient died on the eighth day after the operation. In 36 instances death resulted from a condition which was present at the time of the abortion and which in most cases had been recorded as the indication for the interruption of pregnancy. Of these 36 women, 15 died of cardio-vascular-renal disease in one form or another, ten of tuberculosis, six of cancer, two of Hodgkin's disease, and one each of myelogenous leukemia, chorionepithelioma, and epilepsy. In six cases the cause of death was a disease apparently unrelated to the preceding pregnancy or abortion. None of these deaths occurred before the seventh month after the operation. One woman committed suicide three months after having undergone therapeutic abortion because of pulmonary tuberculosis.

Twelve resident women died within the first month after the operation, corresponding to a fatality ratio of 3.9 per thousand, or one in 250. This is approximately comparable to a fatality ratio of 7.4 per thousand in Sweden, 1939-1945, where 40 deaths were reported among 5,423 legal abortions.<sup>10</sup> It should be noted that of the twelve deaths in the first month five were due to the disease which led to the interruption of pregnancy, rather than to the operation as such. Of the seven deaths ascribed to the operation, six followed hysterectomy and one hysterotomy. Fibroids were recorded as the indication in five of the

seven cases. Since there had been 458 hysterectomies and 257 hysterotomies involving resident women the fatality ratio for these types of operations was on the order of 1 per cent. No death resulting from the operation as such was found following dilatation and curettage.

TABLE VII. DEATHS FOLLOWING THERAPEUTIC ABORTIONS BY CAUSE AND INTERVAL AFTER OPERATION

	FIRST MONTH	2ND-12TH MONTH	SECOND YEAR	TOTAL
<i>Death Ascribed to Operation.—</i>				
Shock	2	-	-	2
Pulmonary embolism	3	-	-	3
Ileus	1	-	-	1
Meningococcus meningitis and pneumonia	1	-	-	1
	7	-	-	7
<i>Condition Present at Abortion.—</i>				
Cardio-vascular-renal	5	6	4	15
Tuberculosis	-	7	3	10
Cancer	-	3	3	6
Other	-	3	2	5
	5	19	12	36
Disease Apparently Unrelated	-	3	3	6
Suicide	-	1	-	1
Grand total	12	23	15	50

### Summary

Almost 3,600 therapeutic abortions were registered as fetal deaths in New York City during 1943-1947. The incidence of the operation, as reported, was about one per 200 known pregnancies and much higher among older than among younger women. Six-sevenths of all interruptions were performed during the first trimester of pregnancy. Conditions most frequently recorded as indications were heart disease, fibroids, mental disorder, the toxemias of pregnancy, and tuberculosis. Psychiatric indications showed a strong upward trend. Four-fifths of the abortions involving fibroids were accomplished by hysterectomy, and almost nine-tenths of the others by dilatation and curettage. One patient in 250 died within one month after the operation.

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## DYSGERMINOMA OF THE OVARY

### An Analysis of 427 Cases

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**D**YSGERMINOMA is a specialized form of ovarian tumor, being of dysontogenetic origin and presenting no specific signs or symptoms other than those usually associated with any enlarging intrapelvic neoplasm. Its absence of hormonal effects is in keeping with the neutral character of the undifferentiated cells participating in its histogenetic formation.

In an analysis of the ovarian tumors for a ten-year period at Kings County Hospital, the incidence of dysgerminoma was found to be 1.1 per cent of ovarian neoplasms, solid and cystic, and 4.7 per cent of primary ovarian malignancies.

The authors are herewith reporting seven cases of dysgerminoma which have come under their observation. In addition, we have collected information on 420 cases of dysgerminoma previously reported in the world literature, and the statistical data of these are presented.

The incidence by age groups, as noted in Table I, reveals that 72 per cent of dysgerminomas have occurred in the second and third decades of life. The youngest patient was 2 years of age<sup>1</sup>; and there have been six patients, 5 years old or younger. The oldest patient on record was 69 years of age,<sup>2</sup> but we are reporting a case of dysgerminoma found at autopsy in a woman 76 years of age.

In the series compiled by the authors, 50.1 per cent of dysgerminomas were found in the right ovary as compared to 35.1 per cent in the left. In 14.6 per cent, the tumors were bilateral. Torsion of the pedicle was reported in 5 per cent of cases.

TABLE I. INCIDENCE BY AGE GROUPS

AGES	NUMBER OF PATIENTS	PER CENT
1 to 10 years	28	6.89
11 to 20 years	155	38.17
21 to 30 years	139	34.18
31 to 40 years	49	12.06
41 to 50 years	22	5.41
51 to 60 years	7	1.72
61 to 70 years	5	1.23
71 to 80 years	1	0.24
Not stated	21	

The association of dysgerminoma with other tumors and with diseases of the genital tract is noted in Table II. In addition, six patients had pulmonary tuberculosis, while another was being treated for lupus vulgaris and a tuber-

culous lymphoma. In eleven cases, dysgerminoma was first recognized during pregnancy. Obstruction to vaginal delivery was encountered in six, and these patients were delivered by cesarean section.

TABLE II. INCIDENCE OF ASSOCIATION WITH OTHER TUMORS OR DISEASES OF GENITAL TRACT

Follicular cysts of ovary	3 cases
Dermoid cyst of ovary	2 cases
Ovarian cyst, type not stated	8 cases
Papillary cystadenoma of ovary	1 case
Pseudomucinous cystadenoma of ovary	1 case
Granulosa-cell tumor of ovary	2 cases
Adenocarcinoma of ovary	1 case
Teratoma of ovary	3 cases
Pelvic tuberculosis	2 cases
Fibromyomas of uterus	15 cases

Despite the large number of reports of patients with dysgerminoma now recorded in the literature, follow-up of these patients has been rather inadequate and statistical comparison therefore is limited. Nevertheless, for eighty patients, a five-year-or-more cure has been noted, an incidence of 27.3 per cent. Cure was complete fifteen years and longer for fourteen patients, or 4.8 per cent. Of the eighty-eight patients reported to have succumbed to the tumor, 75.6 per cent died within the first year after primary surgical treatment. A summary of the end results for patients with dysgerminoma is presented in Table III.

TABLE III. END RESULTS

<i>1. Patients With Dysgerminoma Reported as Having Died During or After Treatment.—</i>	
Died unoperated upon	6 cases
Died within 2 weeks	7 cases
Died within 1 year	55 cases
Died later than 1 year	20 cases
Died from other causes	18 cases
<i>2. Patients With Dysgerminoma Reported as Alive and Well.—</i>	
Follow-up for less than 1 year	46 cases
Follow-up 1 to 5 years	90 cases
Follow-up 6 to 10 years	46 cases
Follow-up 11 to 15 years	19 cases
Follow-up 15 years or more	14 cases
<i>3. Patients With Dysgerminoma.—</i>	
Not traced	106 cases

The prognosis for dysgerminoma when confined to one ovary with an intact capsule as compared with bilateral dysgerminomas or with clinically malignant tumors varies considerably, as demonstrated in Table IV.

TABLE IV. PROGNOSIS BASED ON EXTENT OF DISEASE

	NO. OF CASES	ALIVE 5 YEARS OR MORE	PER CENT SURVIVAL
Confined to one ovary, capsule intact	49	44	89.79
Bilateral	17	5	29.41
Evidence of metastases or infiltration at operation	79	20	25.31

Ascites is also an important sign in estimating the prognosis for patients with dysgerminoma. Hemorrhagic ascites is usually indicative of extensive malignant spread and bears a bad prognosis. Ascites was recorded in sixty-three cases, the comparative end results of which are noted in Table V.

Necropsies have been reported in twenty-six patients with dysgerminoma. In eight, the tumor was found limited to the ovary with no evidence of metastasis. In one, the tumor was bilateral but limited to the ovaries. In those cases where remote metastases were found, the lymph glands, especially the retroperitoneal and periaortic, were generally involved, as were the lungs and liver. Cunningham and McGrath<sup>3</sup> reported that in their patient, 90 per cent of the liver had been replaced by tumor, and metastases were also noted in the lungs, spleen, and pancreas. Metastases to the kidneys were noted by Foderl,<sup>4</sup> Kirschbaum and Newman,<sup>5</sup> Willis,<sup>6</sup> Wolfe and Kaminester,<sup>7</sup> and the authors. Metastases to the lumbar vertebrae were noted by Pendergrass and Selman,<sup>8</sup> and to the lumbar vertebrae and sacrum by Gentil.<sup>9</sup> Willis<sup>6</sup> reported metastases to the dorsal vertebrae which compressed the spinal cord and caused paraplegia. Metastases to the spinal cord were reported by Foderl,<sup>4</sup> while Nittone<sup>10</sup> observed metastases to the facial and acoustic nerves. The thymus, breasts, heart, adrenals, gall bladder, and intestinal tract were noted to be involved on occasion.

TABLE V. RELATION OF ASCITES TO PROGNOSIS

	NO. OF CASES	FOLLOW-UP LESS THAN 5 YEARS. ALIVE AND WELL WHEN LAST SEEN	LIVED 5 YEARS OR MORE	DIED	FOLLOW-UP NOT GIVEN
Clear ascites	14	2	2	4	6
Hemorrhagic ascites	20	0	3	15	2
Type not stated	29	10	8	6	5

Dysgerminoma should, therefore, be classified as a malignant tumor of the ovary, the degree of malignancy varying in each individual case. The potentialities of the tumor to recur or to metastasize are best determined clinically at the time of operation. No apparent correlation exists between the histologic appearance of a dysgerminoma and its degree of malignancy, and the pathologist is unable to predict the malignant potentialities of a dysgerminoma from its microscopic appearance. The prognosis for a patient can be considered good if the tumor is removed early in its development. If no metastases or recurrences are noted at the end of one year after operation, the prognosis is materially improved.

When dysgerminoma appears in a normally developed woman in whom preservation of the childbearing function seems desirable, operation may be limited to simple oophorectomy provided that the tumor is unilateral, presents no capsular perforation, and shows no evidence of local infiltration to adjacent structures or spread to regional lymph nodes. Such a patient, however, should be followed closely thereafter, throughout life, by repeated pelvic examinations at regular and frequent intervals. Any enlargement of the opposite ovary, the appearance of ascites, or subsequent evidence of pelvic infiltration should warrant immediate surgical investigation.

Surgery in all other cases should be radical, including total hysterectomy and bilateral salpingo-oophorectomy. Deep roentgen therapy should be withheld if there is no evidence of tumor spread at the time of surgery, the irradiation being held in reserve in the event that recurrences are noted.

Dysgerminoma of the ovary is highly radiosensitive. Gruss<sup>11</sup> reported a patient with liver metastases found at operation, who was given postoperative irradiation and was alive and well nine years later.

Recently, Russo and Kelso<sup>12</sup> reported the case of a patient with multiple and extensive metastases which regressed in size on intensive and continued therapy with male sex hormone.

A brief résumé of the seven cases of dysgerminoma observed by the authors is herewith presented:

CASE 1.—A 26-year-old white nulligravida was admitted on Nov. 18, 1935. She had received, at another hospital, irradiation therapy to the left mandible because of a tumor diagnosed as reticulum-cell sarcoma. There had been no menstrual irregularities. The patient died ten days after admission. Autopsy revealed bilateral ovarian dysgerminomas, each about 6 cm. in diameter, with multiple metastases to the left mandible, both breasts, the right auricle and the A-V septum of the heart, the liver, the kidneys, the adrenals, the spleen, the gall bladder, the regional lymph nodes, and the serosa of the intestines.

CASE 2.—A 37-year-old white woman was admitted June 7, 1940, complaining of swelling of the abdomen. There had been a weight loss of thirty pounds during the preceding five months. There were no menstrual irregularities. She had been pregnant ten times, having delivered five full-term infants. Her oldest child was twenty-one; her youngest five years of age. Physical examination revealed a right pleural effusion. There was marked ascites; and after paracentesis, at which time 6 L. of clear yellow fluid were withdrawn, an irregular firm mass was palpable to a point above the umbilicus. Death occurred seven days following admission. Autopsy revealed a dysgerminoma of the left ovary, measuring 13 by 8 by 6 inches. The capsule showed no evidence of invasion, and no metastases were noted. Death was ascribed to congestive heart failure.

CASE 3.—A 76-year-old white widow was admitted Jan. 18, 1941, for vaginal bleeding of two weeks' duration. Menopause occurred at the age of fifty. She had borne seven children. On vaginal examination, the uterus was slightly enlarged, firm, and anterior. In the cul-de-sac, a soft, nontender, irregular mass, 7 cm. in diameter, was palpable. At no time was the patient considered a satisfactory operative risk. She expired on Feb. 25, 1941. Autopsy revealed a dysgerminoma of the right ovary with metastases to the left ovary, uterus, and the serosal surfaces of the large and small intestines. There was marked hemorrhagic ascites. The endometrium showed a polypoid hyperplasia. Death was ascribed to generalized arteriosclerosis with myocardial failure and to malignant dysgerminoma of the right ovary with metastases.

CASE 4.—A 13-year-old white girl was admitted March 23, 1939, because of a progressively enlarging abdominal mass present for one year. The menses were regular. Exploratory laparotomy revealed a solid tumor of the left ovary, measuring 25 by 20 cm. The tumor was thought at operation to be a fibroma, and left oophorectomy was performed. The tumor weighed 12 pounds. After the histologic diagnosis of dysgerminoma was made, the patient was given intensive irradiation therapy. Pelvic examination has remained normal, and the patient has remained in good health. She has never menstruated since the irradiation therapy, but she has normally developed secondary sex characteristics.

*Comment.*—The dysgerminoma removed in this case is one of the largest on record. By present standards, it would seem that irradiation therapy was employed unnecessarily. In view of the huge size of the tumor and the fact that the patient had known of its existence for at least one year, it was deemed advisable to give irradiation therapy as a prophylactic measure.

CASE 5.—An 8-year-old white girl was admitted Aug. 20, 1941, complaining of sharp pain in the lower abdomen which had begun suddenly thirty hours before. At exploratory laparotomy, a tumor of the left ovary, 6 cm. in diameter, was found, its long pedicle having undergone six complete revolutions. Hemorrhage into the tumor was noted grossly. A left salpingo-oophorectomy was performed. Histologic study showed a typical dysgerminoma. The patient has been followed at regular intervals since operation. She has never received irradiation therapy. There have been no recurrences.

CASE 6.—A 21-year-old white unmarried woman was admitted Nov. 5, 1944, because of a progressive enlargement of the abdomen first noted six months before. She was mentally deficient. Menses had begun at the age of 17 and were very irregular, recurring two to four



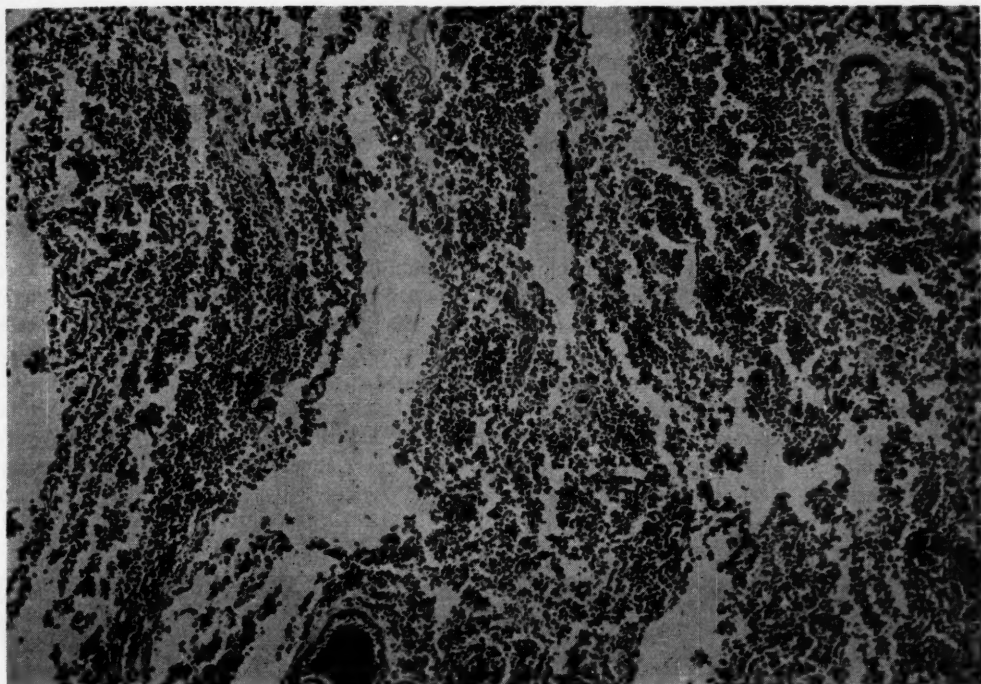


Fig. 1.—Photomicrograph showing section of dysgerminoma described in Case 3. This specimen was removed at autopsy from a 76-year-old woman, the oldest patient on record with dysgerminoma. ( $\times 80$ .)

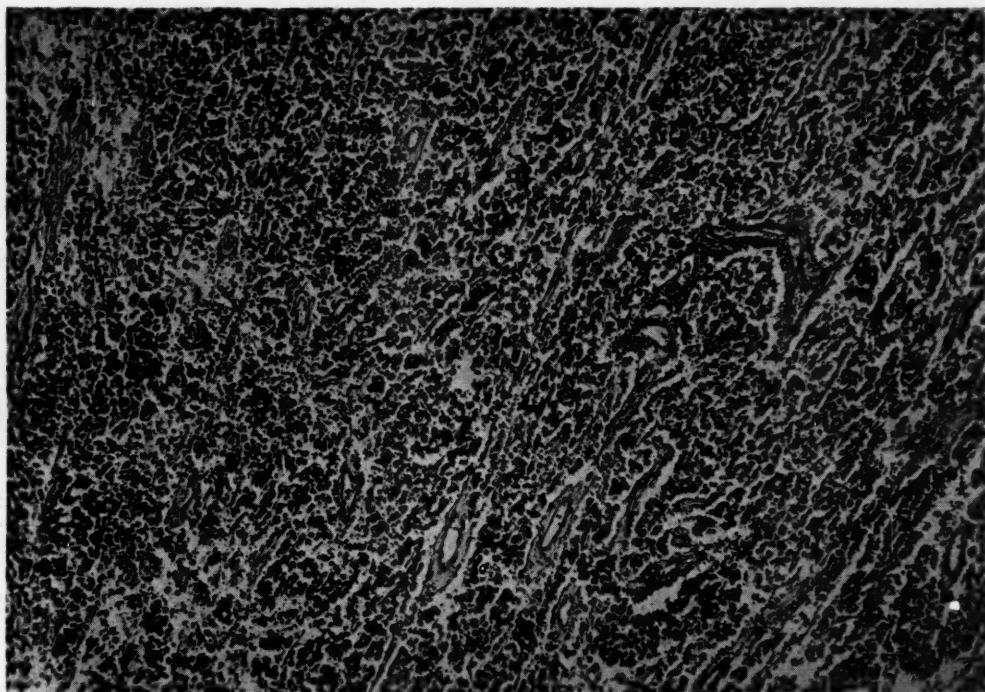


Fig. 2.—Photomicrograph of section of tumor described in Case 4, presenting the typical microscopic appearance characteristic of all dysgerminomas. The dysgerminal cells present a strandlike pattern, the cords of cells being separated by a well-defined fibrous stroma heavily infiltrated with lymphocytes. ( $\times 80$ .)

months apart. Laparotomy revealed a tumor of the left ovary, measuring 15 by 10 by 8 inches. The uterus was infantile with a long cervix and a tiny fundus, the ratio being approximately 3:1. The right ovary was very hypoplastic, being about 1 cm. in diameter. A left salpingo-oophorectomy was performed. A diagnosis of dysgerminoma was made at operation and confirmed by histologic study. No irradiation therapy was given. The patient has remained in good health.

*Comment.*—Although this patient has responded satisfactorily to left salpingo-oophorectomy, more radical surgery could have been done justifiably.

CASE 7.—A 29-year-old white primipara was admitted July 22, 1948. She had been delivered, at term, one year before. At examination six weeks post partum, a tumor thought to be a fibromyoma of the uterus was palpated. The patient did not seek further study until July 21, 1948, at which time the pelvic mass seemed to have increased greatly in size. A tumor of the ovary was then considered, and the patient was referred for immediate operation. At laparotomy, a tumor of the right ovary, 12 by 8 by 8 cm., was found. A total hysterectomy and bilateral salpingo-oophorectomy were performed. Histologic study revealed a dysgerminoma limited to the right ovary. There were follicular cysts of the left ovary. The patient was given intensive irradiation therapy postoperatively. There have been no subsequent recurrences.

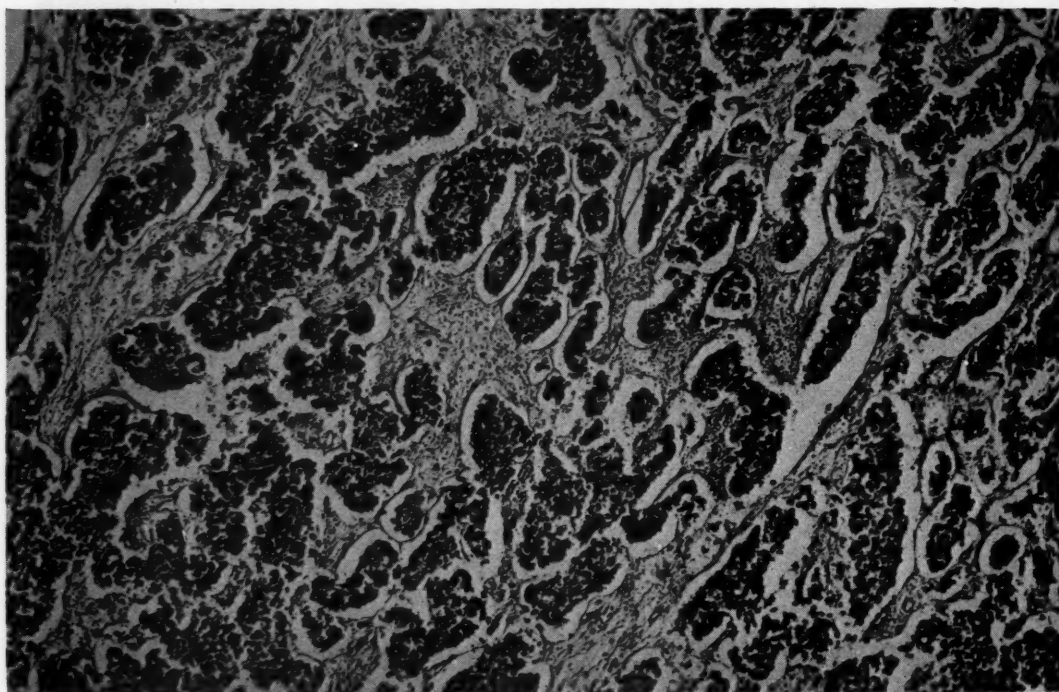


Fig. 3.—Photomicrograph showing an alveolar pattern presented in a section of the tumor described in Case 7. Frozen sections of this tumor were originally interpreted as granulosa-cell tumor, an error readily understandable. This section, stained with hematoxylin and eosin, clearly demonstrates the dysgerminal cell aggregates which are separated by a loose connective tissue stroma infiltrated by numerous lymphocytes. ( $\times 80$ .)

*Comment.*—A frozen section of this ovarian tumor was made at operation; and its interpretation, rendered by a qualified pathologist in collaboration with the patient's husband, also a pathologist, was that of granulosa-cell tumor. Radical surgery was performed in deference to the doctor's and his wife's requests. Surgery for dysgerminoma may be justifiably radical because of the tendency of the tumor to recur or to metastasize if extirpation is incomplete. Irradiation likewise was given as a prophylactic measure.

### Summary

Seven additional cases of dysgerminoma of the ovary have been presented. A complete survey of the world literature has been summarized and statistical data from 427 cases of dysgerminoma have been compared.

The authors wish to express their appreciation to Dr. Samuel Lubin, Brooklyn, for his permission to include one of the above cases in this report.

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## BRENNER TUMOR OF THE OVARY: A CLINICOPATHOLOGIC STUDY OF 31 CASES\*

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SINCE 1907 when Brenner<sup>3</sup> described the three tumors which today bear his name, numerous articles have appeared on this subject, the majority of which have been based on reports of isolated cases or on small series of cases. Eleven cases have been reported previously from the Mayo Clinic.<sup>6, 7, 14</sup> Further search of the files of the clinic revealed a total of thirty-one cases of this interesting tumor. Several recent cases have come within our experience. Therefore, it was thought worth while to review the complete series, with particular reference to clinicopathologic correlation, and to add twenty new cases to the literature. The study was made with the following points in mind: (1) histologic components of the tumor, (2) associated gynecologic disorders, (3) clinical findings, (4) the possibility of diagnosis of the tumor based on these findings, and (5) the treatment necessary to cure the patient having a Brenner tumor.

### Materials and Methods

A review of cases at the Mayo Clinic for a period of thirty-six years from Jan. 1, 1911, to Jan. 1, 1947, revealed that at operation thirty-one patients had been found to have Brenner tumors of the ovaries.

Surgical specimens of the tumors had been preserved in 10 per cent formalin. The gross specimens were secured and studied in detail with special reference to size, shape, color, consistency, and appearance on cut section. Associated gynecologic pathology was considered. Blocks of tumor tissue were removed from the neoplasm and placed in bottles containing fresh preservative.

Blocks were cut by the frozen-section method at 10 microns, stained with hematoxylin and eosin, and mounted for microscopic study (Fig. 1).

### Pathologic Aspects

Grossly the tumors varied in diameter from 0.4 cm. to 19 cm. Nine of the tumors were 1 cm. or less in diameter and were found incidentally at laparotomy. Five of these small tumors were in the hilum of the ovary. In 29 cases the tumors were unilateral, 14 of them being in the right ovary and 14 in the left ovary, while in 1 case the side could not be determined.

The tumor is almost invariably unilateral. Only 15 examples of bilateral Brenner tumors have been reported. In our series there were 2 cases of bilateral Brenner tumors. One of these has been reported previously by Johnson and Dockerty. Grossly the tumors offered little that was distinctive. They resembled ovarian fibromas, being grayish white in color, often lobulated, and, in the solid

\*Abridgment of thesis submitted by Dr. Jondahl to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Obstetrics and Gynecology.



variety, densely hard. On section the tumors cut with little difficulty, and sometimes imparted a gritty sensation owing to calcium deposits. The cut surface showed interlacing whorls and bands of fibrous tissue and occasionally



Fig. 1.—Nests of squamouslike epithelium in dense fibrous connective tissue stroma (hematoxylin and eosin,  $\times 165$ ).

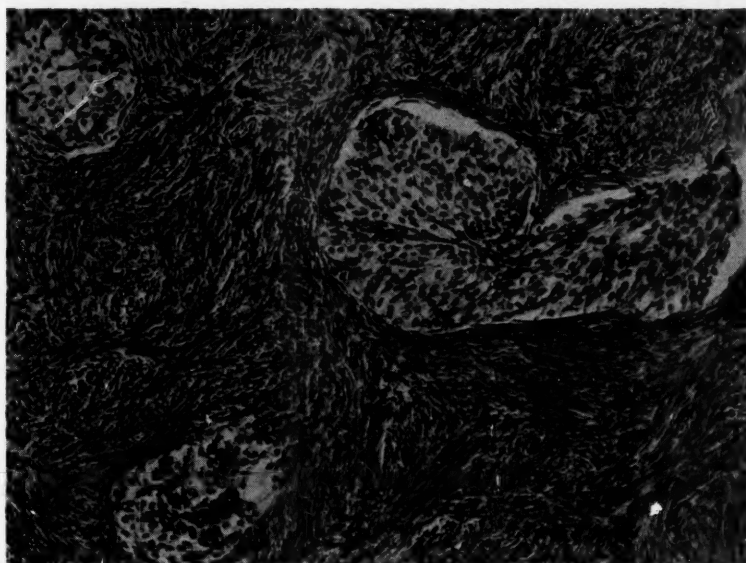


Fig. 2.—Higher power view of cell nests showing some peripheral palisading of the nuclei (hematoxylin and eosin,  $\times 165$ ).

distinct lobulations were produced. Numerous small cystic cavities were seen, which varied from the size of a pinhead to spaces as large as 1 cm. These spaces in the fresh specimen contain an opaque, viscid, yellowish-brown fluid.<sup>9</sup> Adhesions were not seen around the nodules of the tumor. In 24 cases of our series

the tumors were of the solid variety, similar to those of Group A described by Meyer, while 7 tumors were located in the walls of cysts and thus belonged in Meyer's Group B. Of this latter group, 4 tumors were in the walls of pseudo-

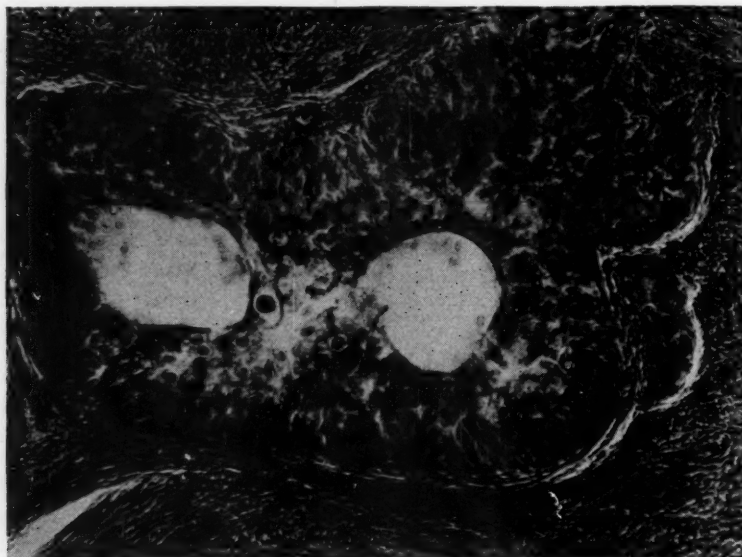


Fig. 3.—Cystic changes in center of cell nest with transformation of squamous cells lining cysts into columnar cells (hematoxylin and eosin,  $\times 195$ ).

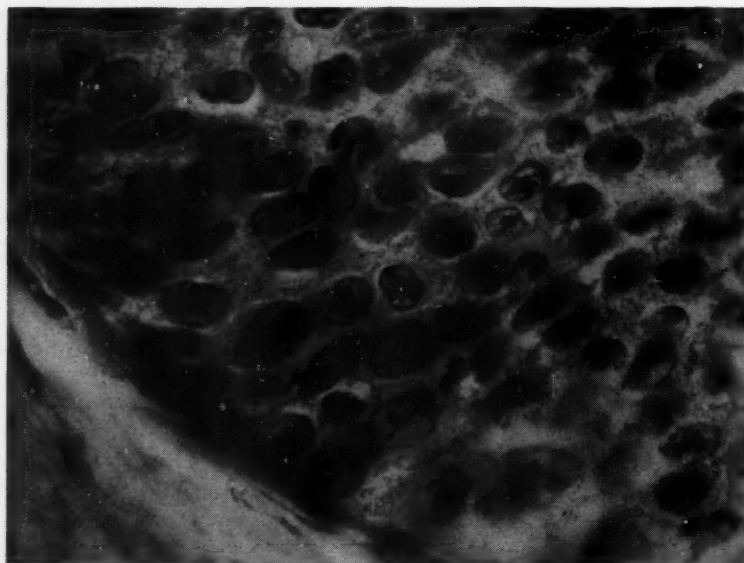


Fig. 4.—Oil immersion view showing typical longitudinal grooving of nuclei. Some cells show two nucleoli, one on each side of longitudinal groove (hematoxylin and eosin,  $\times 765$ ).

mucinous cystadenomas, 2 were in the walls of dermoid cysts, and 1 was in the wall of a teratoma that contained areas of adenocarcinoma, Grade 2, and myxosarcoma, Grade 2.

Microscopically the tumors were found to be composed of abundant fibrillary connective tissue stroma in which were imbedded small nests of compact,

polyhedral squamouslike epithelial cells (Fig. 1). These nests varied in size from 100 to 4,000 microns but for the most part were under 250 microns. An average of 7 nests to each low-power field was observed. The shapes of the nests varied; most of them were round or oval, some were cylindrical, and occasionally branched forms were seen with the branches separated from each other by thin septums. Where these islands were surrounded by the fibrous connective tissue, cellularity was increased and hyaline changes frequently were observed. A "basement membrane" was not evident, but the peripheral row of cells adjacent to the fibrous stroma was frequently palisaded (Fig. 2). Scattered areas of calcification in the stroma were found in 9 tumors.

The centers of the nests were often cystic (Fig. 3) and the cysts were then lined by columnar or cuboidal cells. These cystic spaces, when present, contained mucus and remnants of degenerated cells; the individual cystic units with their contents superficially resembled ova.

Under high power the cells were seen to be polyhedral squamouslike cells. Intracellular bridges or keratohyaline granules were not present. The cytoplasm was abundant, clear or finely reticulated, and was often vacuolated. The nuclei were large, round to oval, and deep staining in comparison to the cytoplasm. The nucleoli were small and two were often present. When this occurred one was located on each side of a longitudinal groove. Varangot,<sup>23</sup> Danforth,<sup>5</sup> and Arey<sup>1</sup> have commented on a characteristic longitudinal grooving or folding of the nuclei, and this phenomenon was present to a varying degree in all of our cases (Fig. 4). Mitotic figures were not seen in any of the 31 cases in our series and all tumors were considered to be benign.

Brenner tumors have to be distinguished from granulosa-cell tumors and from metastatic squamous-cell epitheliomas. With the Galantha stain for mucus this is easy, as granulosa-cell tumors and squamous-cell epitheliomas do not contain mucus but it is always present in Brenner tumors. Granulosa-cell tumors often contain abundant lipid as demonstrated by scarlet red or the Hoerr Romeis stain, while Brenner tumors contain only scant amounts of lipid in the connective-tissue framework and this appears to be part of a degenerative process.<sup>12</sup> Brenner tumors contain glycogen but this substance is lacking in granulosa-cell tumors. The lack of pathologic mitotic figures, epithelial pearls, extension of growth, and a primary site further tend to distinguish this tumor from metastatic squamous-cell epithelioma.

### Associated Gynecologic Disorders

A wide variety of associated lesions was found in our series of Brenner tumors. Some of these lesions were the most significant finding and Brenner tumors were only incidental, while in other cases the Brenner tumor was the chief object of interest.

Twenty-five uteri were available for study. Multiple fibromyomas were found in 15 cases and chronic cystic cervicitis was present in 13. The endometrium was found to be atrophic in 6 cases, hypertrophic in 3, and cystic in 3. There was an endometrial polyp in each of 4 cases and a cervical polyp in 1. Malignant neoplasms were exhibited in 2 uteri, 1 tumor being a squamous-cell epithelioma, Grade 2, of the cervix, and the other an adenocarcinoma, Grade 2, of the fundus.

In 15 cases the Fallopian tubes showed chronic salpingitis. Hydrosalpinx was noted twice, being bilateral in one instance. In 1 case bilateral salpingo-oophoritis was present and in another tuboovarian abscess. In 2 cases a cyst of Morgagni was found and in 1 case a parovarian cyst.

In 4 instances simple cysts were present in the contralateral ovary associated with multilocular pseudomucinous cystadenomas in 3 cases and with multilocular

papillary pseudomucinous cystadenoma in 1 case. Chronic oophoritis occurred in 2 cases and atrophy in 2. In 1 case a dermoid cyst was present with a squamous-cell epithelioma, Grade 2, in the wall, and 1 patient had a small fibroma.

Brenner tumors were found in the wall of a multilocular pseudomucinous cystadenoma four times, in the wall of a dermoid cyst twice. In 1 case the tumor was located in the wall of a teratoma which also contained adenocarcinoma, Grade 2, Myxosarcoma, Grade 2, cartilage, and islands of squamous epithelium. In 2 instances Brenner tumors were present in ovaries which showed evidence of chronic oophoritis.

Adenocarcinoma of the sigmoid and stricture of the sigmoid which developed after irradiation were each found once in association with the pelvic neoplasm.

### Clinical Features

*Incidence.*—In order to estimate the relative incidence of Brenner tumors among ovarian tumors, a survey was made to determine the number of cases of the latter condition at the Mayo Clinic during a ten-year period. About 1,000 such tumors were found. Our study disclosed 17 cases of Brenner tumor in the same period which made a rate of incidence of Brenner tumors of about 1.5 to 2 per cent of all ovarian neoplasms at the clinic.

*Age.*—The youngest patient was 34 years of age and oldest was 76 years of age. Three patients were between the ages of 30 and 39 years, 10 between 40 and 49 years, 9 between 50 and 59 years, 6 between 60 and 69 years, and 3 between 70 and 79 years of age.

*Parity.*—Of the 31 patients all were married except 1. Of the married women 11 had no children, 6 had 1 child, 4 had 2 children, 2 had 4 children, 4 had 5 children, 1 had 6 children and 2 patients had 7 children.

*Menstrual History.*—On review of the menstrual histories of our 31 patients it was found that 15 of these women had had postmenopausal amenorrhea. Five patients had had normal periods; 5, postmenopausal bleeding; 5, menometrorrhagia, and 1 had had oligomenorrhea.

The patients having postmenopausal bleeding presented the following conditions to explain their symptoms: (1) degenerating uterine polyp; (2) carcinoma of the cervix; (3) carcinoma of the fundus; (4) cystadenocarcinoma of the ovary not affected by a Brenner tumor; (5) multilocular cystadenoma with a Brenner tumor in the wall.

Four patients having menometrorrhagia were found to have multiple uterine fibromyomas, and 1 had a multilocular papillary pseudomucinous cystadenoma.

*Symptomatology.*—The commonest chief complaint was abdominal tumor, which was present in 12 cases. In 8 of these 12 cases the tumors were painless; in only 4 cases was pain associated with the tumor. Postmenopausal bleeding was the chief complaint in 5 cases and prolapse of the uterus in 4 cases. Three patients complained of menorrhagia. Three patients had been referred here by the physician in their home town: one had cervical polyp, one, carcinoma of the rectum, and the third patient had exophthalmic goiter. The pelvic tumor of each of these patients was an incidental finding. One patient had an intestinal obstruction that was caused by radiation therapy administered to relieve menorrhagia. The remaining 3 patients complained of backache, polyuria and dysuria, and incontinence on admission to the clinic.

### Preoperative Diagnosis

The preoperative clinical diagnosis was cystic ovarian tumor in 5 cases, solid pelvic tumor in 7 cases, and fibroids in 6 cases. In 4 cases the diagnosis



was pelviabdominal tumor. In 2 cases the diagnosis was prolapse of the uterus with an associated adnexal mass. In 2 cases the diagnosis was prolapse of the uterus with cystocele and rectocele.

In the remaining cases, the following diagnoses were made preoperatively: adnexal mass with fibroids, carcinoma of the fundus, carcinoma of the cervix, carcinoma of the rectum, and radiation stricture of the sigmoid.

### Treatment and Results

*Surgical Treatment.*—Brenner tumor is almost invariably benign, and simple oophorectomy is all that is needed to effect a cure. However, since Brenner tumor is nearly always found incidentally at the time of exploration for an associated pathologic condition, often an extensive amount of tissue has already been sacrificed. If the Brenner tumor is found to be malignant, which is rare, then bilateral salpingo-oophorectomy and total abdominal hysterectomy are indicated.

In our series of cases, unilateral salpingo-oophorectomy was performed five times only. The remainder of the patients underwent additional operative procedures on the pelvic viscera for reasons outlined in the foregoing paragraph.

*Postoperative Follow-Up.*—We were unable to obtain any data on 16 patients after operation; 1 patient died on the nineteenth postoperative day of carcinoma of the sigmoid; 1 patient died five months postoperatively of malignant teratoma; follow-up data on 1 patient could be secured for four months only but she was alive and well at the end of that time; 1 patient was alive and well at the end of a year; 2 patients were alive and well at the end of four years; 2 were well at the end of five years; 1 was living at the end of six years; 1 patient died seven years after Wertheim hysterectomy had been performed for carcinoma of the cervix; 1 patient was well ten years after operation; 1 patient died suddenly of unknown causes eleven years after the Brenner tumor was removed; 1 patient lived seventeen years and one eighteen years after operation. The longest duration of life after surgical intervention has been twenty-five years with no evidence of recurrence of the tumor.

No evidence was found in any of our cases that Brenner tumor had contributed to the death of the patient, and no recurrences were found among the patients regarding whom follow-up data could be secured.

### Comment

Brenner tumor has been considered a relatively rare neoplasm of the ovary. Undoubtedly many cases have been overlooked or were not diagnosed before the nature of this tumor became well known. In our series, 15 of 31 cases were diagnosed incorrectly prior to 1936. From 1911 to Jan. 1, 1947, 31 cases were entered in the files of the clinic. Eleven of these cases have been reported previously which brings the total number of authentic reported cases up to 297.

While it is impossible to prove definitely the histogenesis of the Brenner tumor it is of interest that in 7 of our 31 cases Brenner tumors were intimately associated with neoplasms regarded as being teratomatous in origin. Four of these were in the walls of pseudomucinous cysts, 2 were in the walls of dermoid cysts, and 1 was in the wall of a malignant teratoma.

The age incidence includes practically all decades. The youngest patient with this tumor mentioned in the literature, in the case of Lordy and De Camargo,<sup>16</sup> is a girl 6 years of age. Geissler<sup>10</sup> reported the case of a woman 81 years of age. Giaccone<sup>11</sup> found that in 186 authentic cases of Brenner tumor 50.5 per cent of patients were more than 50 years of age. In our series 18 patients were more than 50 years of age.

Brenner tumor itself apparently did not affect fertility of the patients as each of 19 patients had given birth to 1 child or more. The 11 married patients who had no children had many associated lesions to explain their infertility.

In no instance in our series was the Brenner tumor itself thought to have had any influence on the menstrual period and most authors have concluded that this neoplasm is without endocrine function.

The Brenner tumor itself does not give rise to symptoms unless the growth becomes large enough to produce mechanical symptoms of compression or even torsion, comparable to those of other pelvic tumors. Bloch<sup>2</sup> and Peale<sup>19</sup> have both reported cases in which torsion of the tumor was present. In his case Bloch reported the presence of ascites. Kelemen<sup>15</sup> reported 1 case in which Meigs' syndrome was present. Novak and Jones<sup>17</sup> reported 3 cases of Brenner tumor in conjunction with pregnancy while Siegel<sup>21</sup> and Rogers<sup>20</sup> each reported a similar case. In Siegel's case the tumor produced dystocia and was removed at the time of cesarean section. In most cases reported in the literature as well as in our series of cases, the associated pathology caused the symptoms that brought the patient to the physician and the Brenner tumor was an incidental finding at operation or necropsy. The fact that in 15 of our cases the patient had multiple uterine fibromyomas, that 15 had chronic salpingitis, and that 13 patients had chronic cystic cervicitis was interesting.

The benignancy of Brenner tumors has been emphasized by most authors. However, Dubrauszky and Massenbach<sup>8</sup> have reported the case of a woman 70 years of age, in which a definite transition of benign epithelium to malignant cells was found. No follow-up was noted. Von Numers<sup>18</sup> has recently reported 2 cases in which malignancy existed in Brenner tumors that had occurred in the walls of pseudomucinous cystadenomas. Both of these patients were dead within one year after operation. Mitotic figures have been reported in the epithelium of Brenner tumors by Hartz,<sup>13</sup> Brewer and Jones,<sup>4</sup> and Smith.<sup>22</sup> Hartz, however, stressed the fact that the presence of mitotic figures is not necessarily a sign of malignancy since he has observed them frequently in benign leiomyomas.

In one case of Brenner tumor in which slides were sent to the clinic for confirmation, definite microscopic evidences of malignancy were present.

### Summary and Conclusions

Twenty new cases of Brenner tumor have been added to the literature, and a clinicopathologic study of 31 consecutive cases at the Mayo Clinic from Jan. 1, 1911, to Jan. 1, 1947, has been presented.

The majority of patients having Brenner tumor are in the postmenopausal age group. In our series, 18 of our patients were 50 years of age or older. The tumor does not have definite predilection for either ovary; in our 31 cases 14 were in the right ovary and 14 in the left ovary. Two were bilateral and in 1 case the side could not be determined.

Twenty-four of the tumors were of the solid type or Group A described by Meyer, while 7 occurred in the walls of cysts and therefore belonged in his Group B. Of these, 4 occurred in the walls of pseudomucinous cystadenomas, 2 in the walls of dermoid cysts, and 1 in the wall of a malignant teratoma.

The tumors did not show evidence of any endocrine activity. In all cases of postmenopausal bleeding or menometrorrhagia, some other definite pathologic entity caused the symptoms.

A characteristic finding which would make possible a diagnosis of Brenner tumor preoperatively could not be found. The best the physician could say would be "solid ovarian tumor," "cystic ovarian tumor," or "pelviabdominal tumor."

While many associated gynecologic diseases were found in conjunction with Brenner tumors in our series of cases, none were felt to be statistically significant. Multiple fibromyomas occurred in 15 cases, chronic salpingitis occurred in 15 cases, and chronic cystic cervicitis was present in 13.

In all cases in which follow-up data were secured, no recurrences had been found for as long as twenty-five years.

Radical operation is not necessary to cure the patient of this condition unless a malignant tumor is found; simple salpingo-oophorectomy will suffice. However, since associated gynecologic pathology is so often found, other procedures frequently will be necessary.

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## EFFECTS OF VARIOUS ESTROGENIC PREPARATIONS

### IV. Alpha-Estradiol Administered Intraorally in a Polyethylene Glycol Wax: Objective and Subjective Effects in Climacteric Women

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THE present investigation deals with the buccal administration of alpha-estradiol in a polyethylene glycol wax (hereinafter called buccal estradiol or buccal estrogen). This is prepared as a tablet containing either 0.1 or 0.25 mg. of the hormone.\* It is placed between the teeth and the buccal mucosa and allowed to remain until completely dissolved. Dissolution and subsequent absorption through the systemic circulation occur slowly.

#### Subjects

Our study of the effects of buccal estrogen was carried out in nineteen patients varying from 28 to 56 years of age (Table I). Of these women one subject, aged 28 years had been recently surgically castrated. A 30-year-old woman, with marked climacteric symptoms, had not menstruated for three years. A third individual, 32 years old, had been castrated five years prior to the tests. One patient, aged 34 years, had been amenorrheic for two years. A 36-year-old woman had regular menses but evidenced climacteric complaints and another of the same age had had a complete hysterectomy four months earlier. A 38-year-old patient had been a surgical castrate for two years and another subject, aged 39, had symptoms usually associated with the menopause although her periods were recurring regularly. Four women, aged 41, 41, 42, and 45 years, respectively, were menstruating irregularly; they had typical menopausal complaints. Three patients, 43, 46, and 47 years old, respectively, had been surgically castrated within a four-year period and four women, aged, respectively, 51, 51, 53, and 56 years, were postmenopausal (complete cessation of menses at least eighteen months prior to initiation of therapy). All of the eight latter patients had severe menopausal symptoms.

#### Procedure

A complete history of each patient was obtained at the initial interview. This included a detailed record of the subjective symptomatology. Particular attention was given to an assessment of the degree of the severity of the various complaints. Prior to treatment vaginal smears were taken on several consecutive days in every case. Patients were instructed in the method of obtaining their own smears and were furnished with the necessary supplies for this purpose. Clinic patients reported at weekly intervals and hospitalized subjects were under constant surveillance. Smears were taken daily throughout the period of study, including those days on which the drug was withheld.

\*We gratefully acknowledge our indebtedness to Dr. E. W. Henderson of the Schering Corporation for supplies of the drug used in this investigation.



The initial dosage was varied according to the severity of the symptoms present. In fifteen cases 0.1 mg. estradiol was given as a tablet intraorally for two to three weeks. Three women with more severe complaints received 0.25 mg. in a similar manner. In one instance an initial dose of 0.5 mg. was employed for a period of fourteen days. Whenever more than 0.25 mg. was given daily the dose was divided and spaced evenly over the twenty-four hour period. Maintenance doses varied from 0.1 to 0.75 mg. (one case, No. 2) daily, depending upon the subjective and objective findings. However, in all but one subject (Case 2), therapy was completely stopped for at least one out of every four weeks. The periods of observation of the individual subjects, exclusive of the control periods, varied from 35 to 119 days (Table I).

The methods of collecting the vaginal secretion, making, fixing, and staining the smear, and of recording the data have previously been described.<sup>1</sup> Control smears in each subject were classified as to type with special reference to the presence of cornified cells, superficial cells of both the basophilic and acidophilic type, pyknosis and vesicularity of nuclei, and so forth (Table I). Cornification of the vaginal epithelium is generally used as an index of the intensity of hormonal activity due to endogenously produced as well as exogenously administered estrogen. Therefore, attention has been paid not only to changes in the vaginal mucosa indicating maturation of the epithelial layers but also, and in particular, to the cornification observed during the period of study.

### Results

**A. Objective.**—The vaginal smears of two subjects (No. 5 and No. 7) showed no alteration from the controls after doses totaling 4.9 and 3.9 mg. covering 49 and 28 days, respectively. One patient (No. 8), whose control smears indicated a normal cycle, responded with irregular cornification of the vaginal mucosa. Of four other patients (No. 9, No. 10, No. 11, No. 13) who were menstruating at irregular intervals, three had smears in which the percentage of cornified cells varied somewhat from day to day and from week to week: the other subject (No. 11), who had had her last menstrual period three months prior to initiation of therapy and whose control smears showed some evidence of cornification, started to menstruate after taking 2.2 mg. of estradiol. Thereafter her periods followed at twenty-eight day intervals and the vaginal smears taken throughout the course of therapy resembled those of a normally menstruating woman. One subject, who had been amenorrheic for two years (No. 4) started to flow fourteen days after the hormone was first administered; at that time she had taken a total of 3.5 mg. of the drug. Cornified cells totaled approximately 40 per cent of all cells observed in her smears after 1.0 mg. of the estrogen had been taken.

Eleven patients had smears in which the maximum percentage of cornified cells varied from 10 to 30 per cent following total doses ranging from 0.6 to 9.95 mg. Despite continuance of therapy in all of the eleven instances, no further increases in cornification were observed. The degree of cornification tended to fluctuate somewhat but appeared to remain in the vicinity of the maximum for each individual. In one instance (Case 2) daily doses of 0.25 mg. produced only minor objective and no subjective effects. Therefore the amount was still further increased and when 0.75 mg. estradiol were employed daily her smears gave evidence of an increasing number of cornified cells and these represented approximately 60 per cent of all cells present after a total of 19.75 mg. of hormone had been administered.

**B. Subjective.**—Four women treated as previously described obtained complete relief of all climacteric symptoms. The amounts of estrogen necessary to

TABLE I. EFFECTS OF INTRAOCCALLY ADMINISTERED ALPHA-ESTRADIOL IN 19 WOMEN WITH CLIMACTERIC SYMPTOMS

CASE NO.	AGE IN YEARS	STATUS*	TYPE OF SMEAR DURING CONTROL PERIOD†	NO. ‡ DAYS OBSERVATION	ADMINISTRATION OF A-ESTRADIOL				MAX. CORNIFICATION§			MAX. SYMPTOMATIC RELIEF	
					TOTAL DOSE (MG.)	DAYS USED	INITIAL DAILY DOSE (MG.)	DAILY MAINTENANCE DOSE (MG.)	PER CENT OF CELLS	TOTAL DOSE TO PRODUCE (MG.)	DEGREE¶	TOTAL DOSE TO PRODUCE (MG.)	
1	28	S.C.	2	97	15.75	21	0.1	0.25	30	1.9	marked	4.0	
2	30	A.	3	98	43.75	21	0.25	0.5	60	19.75	slight	22.75	
3	32	S.C.	2	50	6.25	21	0.1	0.25	20	1.8	questioned		
4	34	A.	5	63	7.50	14	0.25	0.1	40	1.0	complete	1.4	
5	36	M.	3	56	4.9	49	0.1	0.1	n.c.		marked	3.3	
6	36	S.C.	4	91	7.7	77	0.1	0.1	20	4.2	marked	2.1	
7	38	S.C.	4	35	3.9	14	0.1	0.25	n.c.		slight	2.5	
8	39	M.	5	35	2.8	28	0.1	0.1	i.c.		marked	1.2	
9	41	Me.	5	84	8.4	14	0.1	0.25	i.c.		moderate	5.2	
10	41	Me.	5	70	8.05	14	0.1	0.1	i.c.		marked	4.25	
11	42	Me.	3	119	14.0	21	0.1	0.1	r.m.		complete	5.1	
12	43	S.C.	2	105	30.0	21	0.1	0.25	i.c.		slight	1.4	
13	45	Me.	5	84	10.85	21	0.1	0.25	10	2.0	complete	14.7	
14	46	S.C.	2	105	24.15	14	0.5	0.25	30	9.95	marked	7.3	
15	47	S.C.	3	119	9.1	91	0.1	0.1	25	0.6	marked	4.2	
16	51	P.M.	4	91	5.4	21	0.1	0.1	30	7.05	complete	10.3	
17	51	P.M.	1	30	16.1	21	0.1	0.25	20	5.15	no change		
18	53	P.M.	2	58	12.75	51	0.25	0.25	25	7.0	marked	6.5	
19	56	P.M.	2	105	14.7	14	0.1	0.1	20	11.5	complete	11.9	

\*Status:

S.C.—Surgical castrate

A.—Amenorrhea

M.—Menstruating at regular intervals

Me.—Menstruating at irregular intervals

P.M.—Postmenopausal (menses ceased at least 18 months prior to therapy)

†Type of smear (control):

1—Basal type cells (atrophic)

2—Intermediate and superficial cells, no cornification

3—Superficial cells, no cornification

4—Approximately 5 to 10 per cent cornification

5—Varying degrees of cornification (not cyclic)

‡Exclusive of control period.

§n.c.—no change

i.c.—irregular cornification

r.m.—irregular menses (see text)

¶Onset of menses fourteen days after therapy started. Smears thereafter were those of a woman with normal cyclic activity.

||Degree of symptomatic relief: slight—partial alleviation of one or more symptoms; moderate—partial alleviation of all complaints; marked—complete alleviation of some, partial relief of other complaints; complete—a return to normal well-being.

produce this effect varied from 3.1 to 14.7 mg. In only one instance did withdrawal of the hormone for a period of one week result in a return of symptoms, although not in as severe a degree as had been previously noted. In another case, that of the 34-year-old subject who had had amenorrhea (Case 4), complete alleviation of symptoms coincided with the onset of menses. Eight women reported marked relief of all symptoms after taking amounts of estradiol ranging from 1.2 to 7.3 mg. One patient noted moderate improvement after 5.2 mg. of the drug had been administered; but all of her symptoms were not controlled even after long-continued therapy. Despite gradually increasing doses of the estrogen, three patients obtained only slight benefit subjectively. In one, this occurred after a total of 1.4 mg., in the second after 2.5 mg., and in the third after 22.75 mg. estradiol had been administered. The nature of the subjective findings in one case (No. 3) are listed as questionably related to the climacterium; moreover, the patient was never sure that she had obtained any relief from the estradiol. One subject (No. 17) reported no alteration in her symptoms as a result of the estrogenic therapy (Table I).

### Comment

Cornification of the vaginal mucosa is normally dependent upon endogenous hormonal stimulation. In surgical castrates and postmenopausal women, smears resembling those seen at various intervals of the menstrual cycle may be induced by treatment with any one of a variety of estrogenic preparations. We have previously reported that a single intramuscular or subcutaneous injection of estradiol and/or its esters, in amounts ranging from 1.0 to 5.0 mg., can activate the mucosa even to the extent of reproducing the full cornification seen during the ovulatory stage of the normal menstrual cycle.<sup>1, 2, 3</sup> The persistence of cornification in some degree for periods lasting for from a few days to as long as three weeks following a single injection has also been noted.<sup>1, 2</sup> Such factors as age, the amount of hormone administered, and the not easily determined physiologic, or hormonal status of the individual must enter into the consideration of the effects produced.

A study of the comparable effects of *single* equivalent doses of estradiol given intraorally was not undertaken. The present investigation has been concerned rather with the effects of small daily dosage, which, not surprisingly, varies somewhat in both objective and subjective effects from treatment by the type of injection previously described.<sup>1, 2</sup> Contrasted with the rapidly marked change in the type of smear produced by single injections, albeit in larger amounts, maturation of the vaginal epithelium, following the buccally absorbed estrogen, took place slowly. When the maximum degree of cornification (for each individual) was achieved, it was maintained within fairly constant limits provided medication was continued. We may assume that small daily doses of the hormone, in this menstruum (a polyethylene glycol wax) will, in most instances, build up the vaginal mucous membrane to the degree usually seen in the postmenstrual phase of the normally menstruating woman.

Cases 5 and 7 failed to respond objectively after taking a total of 4.9 and 3.9 mg. of estrogen, respectively. It may be that these subjects require massive dosage in order to effect changes in the vaginal wall. The two amenorrheic patients are of special interest. Case 2 had not menstruated in three years. Gynecological examination revealed no abnormalities; no infection was present. The patient was extremely nervous but no psychoneurosis or emotional imbalance appeared to exist. It was only after a total of 19.75 mg. of estrogen had been administered in daily doses of 0.25, 0.5, and 0.75, for twenty-one, seven, and twenty-eight days, respectively, in immediate succession, that cornification of 60 per cent of all cells in the vaginal smear was noted. This objective change



was accompanied by the first slight increase in her sense of well-being. Wary of causing untoward effects, we reduced the dose to 0.5 mg. daily with a resultant decrease in cornification and a return of severe symptoms. Control smears in the other amenorrheic patient exhibited a low degree of cornification (5 to 10 per cent). After receiving a total of 1.0 mg. of the drug this rose to approximately 40 per cent and fourteen days after initiation of therapy (3.5 mg. in total) menses were established. One cannot definitely say whether the state of the vaginal smear represented endogenous and/or exogenous hormonal stimulation. The patient was continued on the lesser amount of 0.1 mg. daily for some time thereafter. Her periods occurred regularly, and when last seen at the clinic, although not under treatment at the time, she had been menstruating regularly at twenty-eight day intervals for several months.

In none of the women who were menstruating irregularly could a true approximation of the objective effects of therapy be made. The fluctuations in the percentage of cornified cells observed in the daily vaginal smears varied; they were neither cyclic in nature nor could they be correlated with the various levels of dosage used. We attribute these variations to the fact of both endogenous and exogenous estrogen acting simultaneously.

No toxic or untoward reactions to the drug were encountered. With one exception, all of the patients treated with alpha-estradiol in tablet form stated a preference for this over other methods of therapy. The symptomatic relief varied in degree but generally bore a definite relation to the length of time the drug was used and the amount administered. The one woman who did not respond subjectively to treatment was psychotic and therapy had to be terminated because it became necessary to discharge her to another institution for psychiatric care. It was noted that those women who responded with lesser degrees of symptomatic relief were emotionally disturbed by financial or marital troubles.

Climacteric patients treated with a single injection of 1 mg. or more of estrogen have reported varying degrees of symptomatic relief starting one to three days after injection.<sup>2,3</sup> Small daily doses of the intraorally administered drug alleviated climacteric symptoms slowly. We believe the period of time needed to achieve a sufficiently high blood and tissue level of estrogen to be the cause of the less rapid response. This observation suggests that, in clinical use, it may be wise to initiate therapy with one or more massive parenteral doses of hormone and to determine the maintenance dose once the patient is symptom free.

### Summary

Alpha-estradiol in polyethylene glycol wax tablets containing 0.1 and 0.25 mg., respectively, was administered daily to nineteen women with climacteric symptoms. The tablets were placed between the teeth and the buccal mucosa and allowed to dissolve.

The daily dosage, which varied from patient to patient and from week to week during the periods of observation, ranged from 0.1 to 0.75 mg.

The period of study varied in individual subjects from 35 to 119 days, exclusive of the control periods.

Vaginal smears were taken on several consecutive days prior to initiation of therapy and daily thereafter.

Alterations in the vaginal smears were observed in seventeen cases. Cornification of the vaginal epithelium similar to that seen in the postmenstrual



phase of the cycle of normally menstruating women was noted. Lesser amounts of hormone or withdrawal of the drug caused a decrease in the total number of cornified cells.

Eighteen women reported alleviation of climacteric symptoms. The relief varied in degree from slight to complete.

No toxic manifestations of this estrogen administered intraorally in polyethylene glycol wax were noted.

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## AN EVALUATION OF THE SYMPTOMS AND SIGNS IN ECTOPIC PREGNANCY, BASED ON AN ANALYSIS OF 130 CASES

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THIS study was undertaken to determine the frequency of the so-called textbook syndrome of ruptured ectopic pregnancy in a series of 130 consecutive cases at the Massachusetts General Hospital during the ten-year period, 1937 to 1946. An effort was made to establish the incidence of the four cardinal manifestations of a ruptured extrauterine pregnancy, i.e., pain, bleeding, amenorrhea, and the presence of a pelvic mass, as they occurred in these average unselected cases.

Early in the survey of these cases it became apparent that there were two clinical syndromes which occurred with sufficient frequency to justify their distinction on the basis of symptomatology, differential diagnosis, and treatment.

Traditionally the classic picture of *extrauterine* pregnancy centers around the acute condition in tubal rupture with abdominal pain, hemoperitoneum, and the frank manifestations of shock. Although only 15.3 per cent of the patients of this series were admitted in a state of shock, this does not detract from the importance of correct diagnosis and treatment in this group. Older clinicians more expert in physical inspection and diagnosis were prone to suspect such a patient of "bleeding inside." The present tendency to rely less upon observation than on laboratory tests may result in delay in the treatment of such a rapidly progressive internal hemorrhage.

In contrast to the urgency of an acutely ruptured ectopic pregnancy representing a considerable problem in immediate treatment, the majority (85 per cent) of cases in this study were found to present subacute symptomatology. It will be seen that this latter group present essentially diagnostic rather than immediate therapeutic problems requiring a careful history and physical examination plus appropriate laboratory tests.

*Pain.*—This was the most common and apparently the most dependable of pathognomonic manifestations. Pain was present as an entry complaint in 120, or 92 per cent, of cases. It was usually described as sharp or crampy in nature and most often localized to one of the lower abdominal quadrants. Low back pain and low midline or hypogastric pain were not uncommon, however. This pain was severe and of acute onset in the majority, causing the patient to present herself for medical treatment. The complaint of low-grade, crampy pain accelerating over several days to the sharp pain of an impending or actual rupture was not seen so often as the spontaneous onset of severe intermittent or constant lower-quadrant pain. In the cases where it could be determined, pain was the first symptom of the acute illness in 33, or 25.4 per cent.

**Bleeding.**—The presence of vaginal bleeding usually did not correspond with the onset of pain initiating the acute episode. In other words, slight to moderate flowing was often present several days before the appearance of pain. Bleeding, however, was the second most dependable of the four cardinal points, occurring in 109 patients, or 83.8 per cent. As a sign present in the acute episode, bleeding preceded pain in 24.6 per cent of the cases.

It was difficult in many women to determine whether pain or bleeding had prior onset in the acute episode. In the great majority of cases, however, the patient would experience several weeks of intermittent or daily bloody vaginal discharge preceding the attack of pain. Therefore, unless, anteceded by a period of clear-cut amenorrhea, the patient's and often the physician's attention was distracted from the presence of vaginal bleeding by the more insistent pain complaint.

**Amenorrhea.**—The almost universal absence of definite amenorrhea in the majority of cases was one of the most striking findings in this survey. These cases were conspicuous by a history of irregular or intermittent vaginal bleeding often for several weeks prior to the acute illness. Several women sought medical consultation for explanation of this metropathia but many ignored the irregular staining, assuming it was a late or abnormal period.

The principal error noted in the question of amenorrhea was the assumption by both patient and physician that the last menstrual period had been a normal period in all respects.

A typical history may be as follows: The patient states she was four to seven days past the expected menstruation date. Flow then began and continued daily or intermittently for several weeks thereafter, accompanied by a tenderness or dull ache in the lower quadrant and climaxed by the abrupt onset of severe pain requiring hospitalization.

It may be seen that a period of intermittent bleeding several days overdue may easily be interpreted as the last menstrual period. Unless questions are directed specifically to determine what was possibly the last normal menstrual period, it is difficult to arrive at a time estimation which will aid the diagnosis of extrauterine or faulty intrauterine pregnancy.

**Mass.**—The fourth point of the ectopic syndrome has been given as the presence of a palpable lower-quadrant or pelvic mass. In all cases data were obtained from the initial physical examination. Unless a mass was noted by the first examiner it was not recorded as positive. A mass was thought to be present in only 33, or 25.4 per cent, of the cases. It was the general impression that a palpable mass was not a reliable sign and in the majority of cases the diagnosis was felt to be so clear that laparotomy was undertaken without further attempt at delineation of a mass.

**Shock.**—The presence of obvious clinical shock upon admission was noted in only 20 or 15.3 per cent, of 130 cases. Beacham and associates,<sup>1</sup> in a study of 1,059 cases of ectopic pregnancy at the New Orleans Charity Hospital, found 13.6 per cent of patients in shock upon admission.

The dramatic signs of shock are always impressive and may immediately suggest the possibility of an abdominal condition with internal hemorrhage requiring surgery. The rate of bleeding is difficult to estimate other than on the basis of the depth of shock and response to transfusion. Although it is a surgical maxim that it is best not to operate until the blood pressure and pulse have stabilized and the patient is recovering or has recovered from the shock state, to follow this plan may not always be the wise decision. The rate and amount of intraperitoneal hemorrhage may be such that transfusion in the ordinary manner is not sufficient to correct the low circulating blood volume. Cases have been reported in which well-meant delay resulted in exsanguination of the patient before she reached the operating room.

Infusion of a large quantity of blood under pressure as described by Pierce, Robbins, and Brunschwig<sup>5</sup> may quickly bring the patient to an operable state. Otherwise, laparotomy with ligation of the bleeding vessel, despite the patient's critical condition, may be necessary before transfused blood can ameliorate the hemorrhagic shock.

*Pregnancy Symptoms.*—Pregnancy symptoms were most undependable as a diagnostic aid. In 48, or 36.8 per cent, at least one symptom was noted, usually a swelling or tenderness of the breasts. Many multiparas were quite certain they were not pregnant.

*Preoperative Diagnosis.*—The story of a skipped period with vaginal staining, abdominal pain, or shock led to the correct preoperative diagnosis in 55 out of 82 cases (67.6 per cent) from the ward service.

During the same ten-year period (1937-1946) 23 patients were operated upon under the mistaken diagnosis of ectopic pregnancy and other conditions found. Taking into account these 23 cases, the corrected preoperative diagnosis would be 52 per cent. Marchetti<sup>4</sup> reported a correct preoperative diagnosis of 87.9 per cent, but corrected it to 56 per cent when he included the patients with wrong diagnoses of ectopic pregnancy. The differential diagnosis appears to lie between pelvic inflammatory disease, appendicitis, ruptured ovarian cysts, and normal pregnancy.

*Diagnostic Procedures.*—An examination under ether anesthesia and diagnostic dilatation and curettage were carried out in 44, or one-third of the cases. In several patients the surgeon was able to identify an extrauterine mass on bimanual palpation which had not been felt at the entrance examination.

The chief value and usual purpose of the curettage were to detect the presence of decidua or a so-called endometrial decidual reaction. Such a finding was present in 10, or 22.6 per cent, of our patients undergoing this procedure. It is probable that the presence of a decidual reaction is strong presumptive evidence of an extrauterine pregnancy, providing other intrauterine causes, such as incomplete abortion, etc., are excluded. However, the absence of decidua certainly should not refute the diagnosis of ectopic gestation.

The Aschheim-Zondek test was utilized in 40 cases and was positive in three-fourths of this number. The difficulty of the A-Z test, of course, lies in the four- to five-day interval necessary for its performance.

Various miscellaneous procedures were used to supplement the history and physical examination. Peritoneoscopy for the presence of hemoperitoneum and/or pelvic pathology was performed in five cases, in two of which free blood was found in the peritoneal cavity or specific abnormality was observed. Colpotomy for the presence of free blood in the cul-de-sac was carried out twice, giving a positive result in one case.

Although no systematic series of laboratory tests was used in all cases, those which were found to be generally valuable will be mentioned.

The white blood count was commonly determined, but was of significant elevation in only a small number of cases. There was no apparent correlation of white-count response with immediate pelvic pathology. In many cases of acute hemoperitoneum, the time interval was often too short for a pronounced rise in count. On the other hand, in cases of a more chronic nature, the white count was elevated upon admission. Heaton, in reporting the experience at Bellevue Hospital, states that the white count was universally elevated and he also found the sedimentation rate to be definitely elevated in two-thirds of the cases. In our series, the sedimentation rate was not determined in enough cases to be of any significance.



The hemoglobin value was similarly unpredictable. It was of a low value in patients who were admitted in a state of frank shock. In many of these women it appeared that a hematocrit determination would probably have been more informative. In the nonacute or nonshock cases, which represented the majority, the hemoglobin value gave a base line for subsequent therapy.

The febrile response was likewise extremely variable. The highest temperature recorded was 101.2° F. In the cases with hemoperitoneum with or without shock and with or without tubal rupture, the white count response was usually more rapid and dependable than a febrile response.

*Nature of Operative Procedure.*—The diagnosis was proved by operation in every case. There was no operative mortality. No attempt will be made to list the variety of operative procedures. Only those operations which were performed with comparative frequency will be mentioned.

Unilateral salpingectomy was done in 52 cases, or 40 per cent of the total. Unilateral salpingo-oophorectomy was accomplished in 18, or 13.8 per cent. The usual finding in these cases was a tubo-ovarian mass of such extent that an attempt to spare the ovary was either very difficult technically or was considered unwise.

Unilateral salpingectomy and appendectomy were done in 14, or 10.7 per cent. Perhaps the reason why appendectomy was not performed in a greater number of cases was that most operators were reluctant to amputate the appendix in the presence of free blood in the pelvic or general peritoneal cavity. However, no immediate postoperative complications ascribable to the appendectomy were noted in those cases of hemoperitoneum in which this operation was carried out. Unilateral salpingectomy plus uterine suspension was performed in 9, or 7 per cent, with unilateral salpingo-oophorectomy and suspension in 9 additional cases.

*Operative Findings.*—A ruptured ectopic pregnancy with either active bleeding from an opening in the wall of the tube or evidence of tubal rupture with a temporary clot seal was found in 63, or 48 per cent, of the cases. Active bleeding from a ruptured tube was not a common finding at laparotomy. A relatively small perforation, as with a perforation of a tubal viscus in other areas, evidently has a marked propensity for an attempted sealing-off process through either formation of an adherent blood clot or the adhesion of adjacent ovary, omentum, or other contiguous structure.

Hemoperitoneum was found in 87, or 67 per cent, of the series. In many cases the blood was confined to the pelvic cavity. The volume was always difficult to estimate but appeared to vary from 50 c.c. to almost 2 liters.

Incomplete tubal abortion was discovered in 28, or 21 per cent of cases. By this we mean the presence of an unruptured tubal pregnancy which may or may not be attempting to abort via the fimbriated end of the tube when found at laparotomy. So-called impending abortion was found in several cases and often by simply "milking" the tube the ovum could be expressed through the fimbriae, necessitating only a slight plastic procedure to insure tubal patency. There may or may not be active bleeding from the fimbriated end of the tube. In many cases of large hemoperitoneum the cause of bleeding was found not to be the anticipated "ruptured tube"; rather, active bleeding from the free end of the tube was discovered as the only possible cause.

As with any group of cases involving acute gynecologic conditions, several unusual cases were found which may be of interest. Although there were no cases of simultaneous bilateral involvement, four patients gave a history of previous ectopic pregnancy. One apparently normal intrauterine pregnancy estimated at two and one-half months was discovered. There was no miscarriage subsequent to operation in this case. Two interstitial pregnancies were discovered which were treated with wedge-shaped resection of the cornua.

### Comments

It is apparent that of the four so-called pathognomonic signs and symptoms of extrauterine pregnancy lower-quadrant pain was the most constant finding. Pelvic pain varying from an intermittent, low-grade, crampy ache to the sharp, severe pain of the impending or actual tubal rupture occurred in 92 per cent of the patients, or in 10 per cent more than complained of vaginal bleeding upon admission.

Jeff and Winson,<sup>3</sup> in a review of 212 cases, report that, of the classic triad, pain, vaginal bleeding, and one or more missed periods, approximately 80 per cent gave a history of at least two of the three symptoms. Marchetti in studying 141 cases found pain in 98.5 per cent and abnormal vaginal bleeding in 78.7 per cent.

The fact that vaginal bleeding occurred either prior to or concomitant with pain in such a large number of this group is perhaps significant in a syndrome usually thought to be characterized by amenorrhea. Amenorrhea per se, dating from the last menstrual period, or more exactly the last normal menstrual period, was not present with sufficient frequency to determine an accurate percentage. It is suggested that a history of skipped or missed periods is not essential for the diagnosis of ectopic pregnancy.

In many cases the assumption was made, often by both patient and physician, that the most recent episode of vaginal staining, whether regular in the cycle or delayed and scant, represented the last menstrual period. If thus an anomalous period is accepted by the physician as the last normal period, it is suggested that he may fail to obtain the anticipated history of a skipped or missed period attributed to this syndrome.

On the basis of immediate symptomatology and subsequent treatment we have attempted in this series to divide the patients into two groups, i.e., those admitted in shock and those with lower-quadrant pain and vaginal bleeding but not manifesting signs of shock.

Although the shock group is definite in the minority, it is in these patients that ectopic cyesis with uncontrolled hemorrhage can lead to rapid death. Immediate laparotomy with suture of the bleeding vessel may be necessary before the patient will respond to shock therapy.

Fortunately, in the majority of cases, abnormalities were observed for several days preceding operation. Fifty-eight patients, or 48 per cent, not in shock were operated upon the day of admission. The remainder were usually explored within two or three days of admission.

In doubtful cases, the failure of the pain to subside after two or three days of symptomatic treatment, in addition to a progressive anemia and positive contributory findings, such as the presence of decidua on curettage, gave support to the diagnosis and led to subsequent exploration.

Beacham<sup>1</sup> states, "The clinical picture of tubal pregnancy is so typical in many cases that diagnosis is easily made. In others a carefully obtained history and thorough examination of the patient are necessary to prevent diagnostic errors."

### Summary

Analysis of the presenting symptomatology in 130 cases of ectopic pregnancy revealed two clinical groups: those admitted in shock with acute lower-quadrant pain requiring immediate diagnosis and treatment and the nonshock or subacute group composed of the majority (85 per cent) of cases, which were essentially diagnostic problems.

Since the diagnosis in the majority was made from careful interviews regarding history and symptoms, without other diagnostic aids, the symptoms pattern of ectopic gestation is emphasized and important points in the histories of these patients are discussed.

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264 BEACON STREET

## SYSTEMIC PLASMA PROGESTERONE LEVELS DURING THE HUMAN MENSTRUAL CYCLE\*

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IN 1933 Clauberg and associates,<sup>10</sup> employing his assay method, were unable to detect progestational activity in extracts either of 250 to 335 c.c. blood samples drawn during various stages of the human menstrual cycle or in extracts of 12 to 15 c.c. of serum or 300 c.c. of blood from pregnant patients.

The Corner-Allen test for progestin was used by Bloch in 1936<sup>7</sup> to assay extracts of large blood samples. He found no activity in up to 500 c.c. of human pregnancy blood, less than 1 Rabbit Unit of activity in 8 to 12 liters of human pregnancy blood, and no activity in 70 c.c. of rabbit pregnancy blood. In 1940, de Allende<sup>2</sup> reported assays of blood samples drawn at three-day intervals throughout several menstrual cycles of the monkey, *Macacus rhesus*. The results were expressed in terms of the degree of endometrial proliferation on the Me-Phail scale; it was estimated that the blood serum samples contained from 0.06-0.12  $\mu\text{g}$  to 0.25-2.5  $\mu\text{g}$  per cubic centimeter. Subsequently, it was shown that progesterone might be bio-assayed directly by a method which appears to be sensitive, accurate, and specific.<sup>20, 21</sup> The present report describes the results obtained when this method was used to follow plasma progesterone levels throughout part or all of several human menstrual cycles.

### Methods

The blood samples were obtained from four apparently healthy young women, 20 to 30 years old, who reported regular menstrual cycles. The donors were instructed to determine and record their oral temperatures on awaking daily throughout the period during which blood samples were taken. On the mornings of the days indicated in the graphs (Figs. 1, 2, 3, 4), a blood sample of about 1 c.c. was drawn from an arm vein. Each sample was discharged into a 1 c.c. centrifuge tube containing 0.05 c.c. of 20 per cent sodium citrate solution. The tube was inverted several times to insure mixing of the anticoagulant, and the mixture was centrifuged. Immediately thereafter a measured volume of the plasma was added, drop by drop, with stirring, to cold (10° C.) acetone. Subsequent separate incorporation in sesame oil of the "free" (ether and acetone soluble) and "bound" (ether and acetone insoluble precipitate, subsequently hydrolyzed) progesterone fractions was carried out according to a standard procedure.<sup>21</sup> The interval from the time the blood was drawn until the plasma was precipitated in acetone was 35 minutes or less (usually 20 minutes or less) in all but eight of the total of 98 plasma specimens. The assays were conducted according to a standard bio-assay method.<sup>20</sup>

\*This investigation was aided by grants from the Committee for Research in Problems of Sex, National Research Council, and from the James Hudson Brown Memorial Fund of the Yale University School of Medicine.



### Results

Figs. 1, 2, 3, and 4 indicate for each donor (H1, H2, H3, H4) both waking temperatures and progesterone levels. A summary graph compares the various progesterone curves (Fig. 5). It should be noted that on the latter graph the units on the abscissae have been adjusted so that the ordinates for the appearance of progesterone and for the beginning and end of menstruation are simultaneous. Each solid or open circle shows the bio-assay of free or bound progesterone, respectively, in the plasma obtained on the date indicated. In this connection, it cannot be emphasized too clearly that the lines connecting successive circles have been added purely to assist visualization. It by no means can be assumed that the plasma progesterone levels during the time between assays necessarily followed the straight line. Finally, since the assay can demonstrate that insufficient progesterone is present to give a positive reaction but does not reveal the absence of the hormone, a combined circle and arrow symbol is used to indicate that less than the indicated detectable concentration of the hormone occurred.

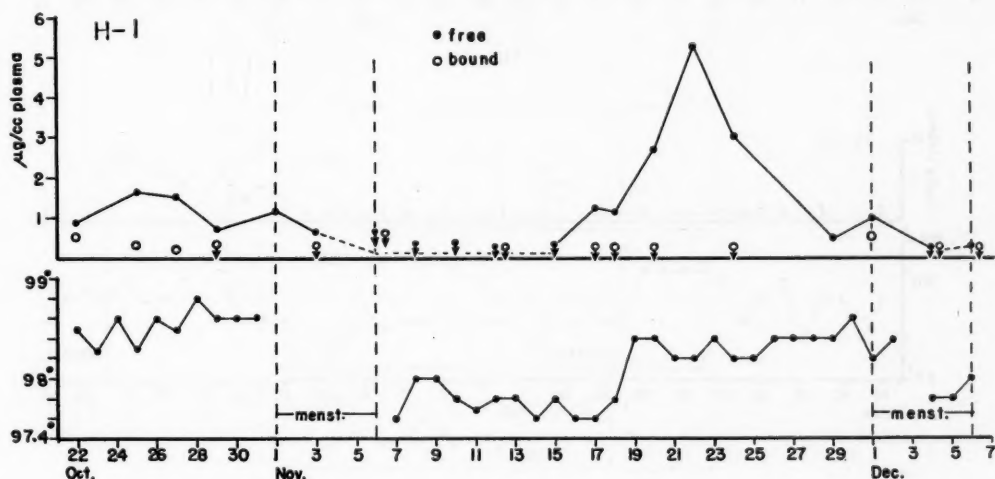


Fig. 1.

#### Free Progesterone.—

*Follicular phase:* With the exception of the 11 June specimen of H4 (Fig. 4), progesterone was not detected during the interval from the cessation of menstruation until close to the time of ovulation.

*Ovulation:* Progesterone appeared a day or two before, or else coincidentally with, the major rise in the waking temperature curve. Such a rise, or the dip which may precede it, is regarded by many observers as signaling the time of ovulation.

*Mittelschmerz* has also been considered by some investigators to coincide with ovulation. This phenomenon occurred during the first study of H4 (Fig. 4). During a later cycle, blood samples were taken beginning at the time when it was judged that ovulation might be imminent, and Mittelschmerz occurred again. This donor took her waking temperatures at about 7 A.M. On 17 February her waking temperature was low, a blood sample subsequently assaying at  $0.9 \mu\text{g}$  progesterone per cubic centimeter plasma was drawn at 11 A.M., and Mittelschmerz was experienced at 11 to 11:30 P.M. On 15 June the waking temperature was low, but the blood sample drawn at 11:30 A.M. contained  $0.45 \mu\text{g}$  progesterone per cubic centimeter plasma. The following day the waking

temperature was still low, the hormone could not be detected in a sample drawn at 10:30 A.M., and Mittelschmerz ensued between noon and 12:40 P.M. The waking temperature was elevated the next day. Thus, in the first instance progesterone was present 12 hours before Mittelschmerz, and in the second

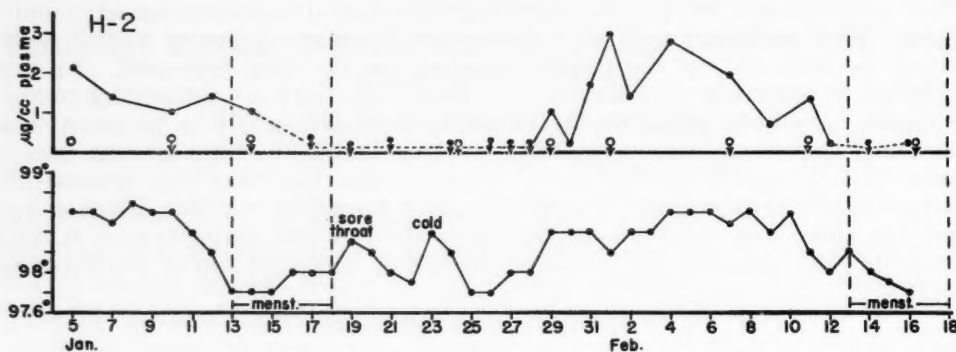


Fig. 2.

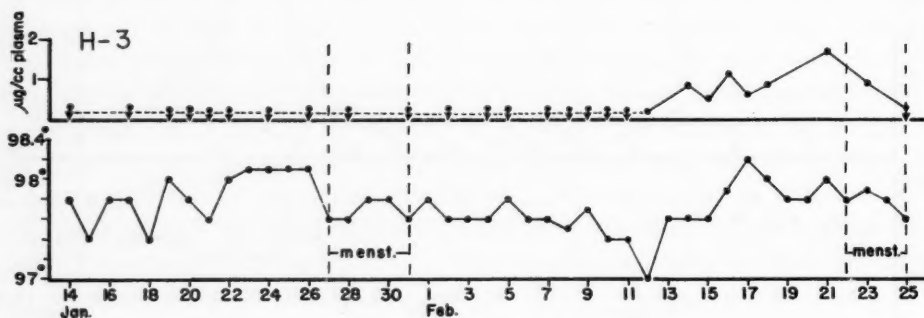


Fig. 3.

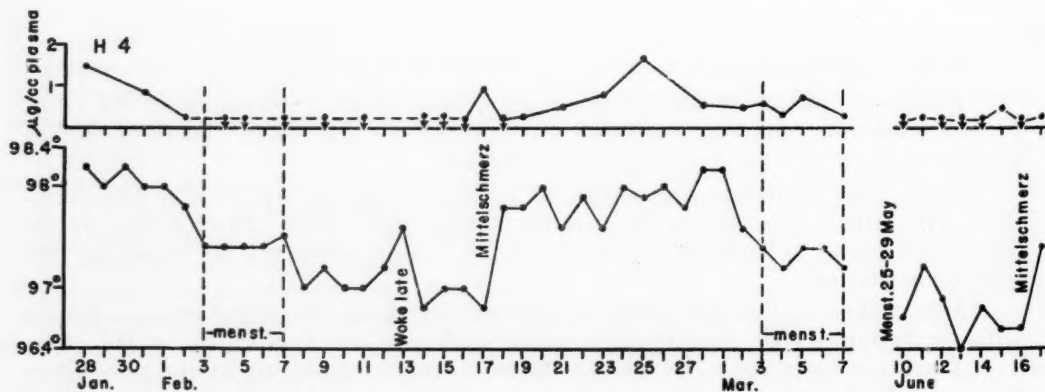


Fig. 4.

instance the hormone was detected 24 hours before, but not one and one-half hours before Mittelschmerz. Further assays showed that the hormone was absent at 12 and present at 36 hours (Feb.), and present at 24 hours (June), after Mittelschmerz. If, for purposes of speculation, the findings for the two

episodes are arbitrarily combined, it can then be said that the hormone was present 24 and 12 hours before Mittelschmerz, was absent one and one-half hours before and 12 hours after the phenomenon, and was present again 24 and 36 hours (and longer) after Mittelschmerz was noted.

Finally, it is apparent that the progesterone level invariably fell on the day after the hormone first appeared (H1, 18 Nov.; H2, 30 Jan.; H3, 15 Feb.; H4, 18 Feb.), then rose again the following day.

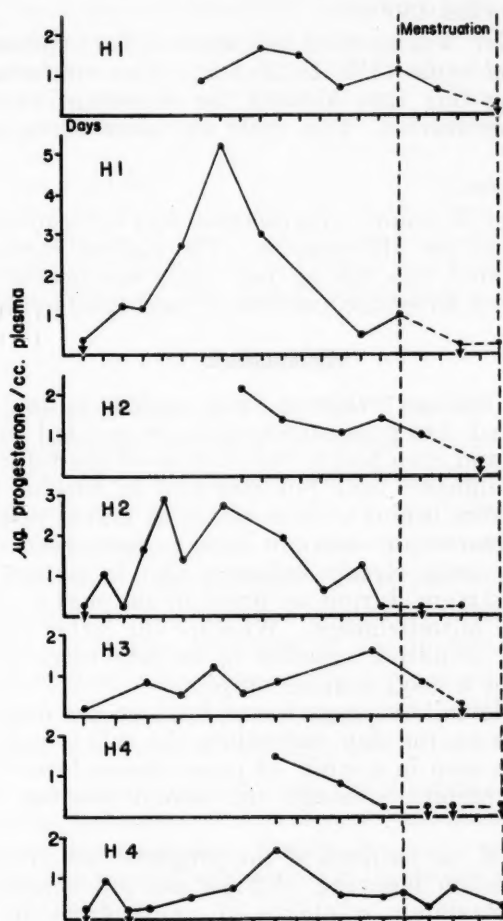


Fig. 5.

*Luteal phase:* While the curves for progesterone levels during the luteal phase of the cycle obviously vary, it may be said that the general pattern appears to be that of a simple rise and fall. Maximal concentrations of the hormone on the curves ranged among the donors from 1.7 to 5.2  $\mu\text{g}$  per cubic centimeter plasma.

*Period of menstruation:* Progesterone levels were determined before and during eight menstrual periods. One such period followed what was presumably an anovulatory cycle (H3, Jan.; see below). For two other periods (H2, Feb.; H4, Feb.) it is not evident whether progesterone was present when bleeding began. The hormone clearly was present at the onset of the other five periods in concentrations from 0.65 to (probably) 1.4  $\mu\text{g}$  per cubic centimeter plasma

(see graphs), and in four of these cases persisted for one day (H2, Jan.; H3, Feb.), two days (H1, Nov.), or four days (H4, Mar.) thereafter.

**Waking temperature:** Comparison of the waking temperature curves and the progesterone curves shows a close coincidence of elevated temperature and the presence of progesterone, both during the luteal phase and during the menses. Major temperature elevations during the follicular phase coincided with the occurrence of a sore throat (H2, 19-20 Feb), a cold (H2, 23-24 Feb.), and an occasion when a donor awoke to realize that she had overslept about two hours and was late for work (H4, 13 Feb.).

**Anovulatory cycle:** The unusual temperature fluctuations during the latter part of one menstrual cycle (H3, 14-26 Jan.) were confusing. Assays of the samples taken during this time showed the consistent absence of detectable concentrations of progesterone. This cycle was assumed to have been probably anovulatory.

**Bound Progesterone.—**

The concentration of bound progesterone was determined in 14 of the H1 samples and in nine of the H2 samples. The highest concentration of bound progesterone encountered was 0.5  $\mu\text{g}$  per cubic centimeter plasma; only two other samples contained detectable amounts of the bound hormone.

### Discussion

On the basis of indirect evidence from various animal species it has repeatedly been suggested that progesterone may be secreted before the formation of the corpus luteum and even before the rupture of the follicle.<sup>19, 20, 28</sup> In fact, van der Horst and Gillman<sup>27</sup> have reported that in *Elephantulus*, the elephant shrew, the corpus luteum begins to form prior to, and is responsible for, ovulation, but a similar observation does not seem to have been made in any other species. The present study clearly indicates that in women progesterone may appear in the blood stream during or prior to the major rise in waking temperature and prior to Mittelschmerz. Whether the latter two phenomena coincide temporally with ovulation remains to be demonstrated, although such a viewpoint has received a good deal of support.<sup>4, 11, 12, 13, 17, 23, 24, 26</sup> The significance of the invariable fall in progesterone level on the day after the hormone appeared and the rise on the day succeeding the fall is not yet apparent; the same phenomenon was seen in a study of progesterone levels in beginning pseudopregnancy in two rabbits, although the second rise was delayed in one of these animals.<sup>14</sup>

The significance of the outlines of the progesterone curves is not yet clear. The highest concentration observed (5.2  $\mu\text{g}$  per cubic centimeter plasma) is much less than the maximum solubility of progesterone in saline<sup>15, 18</sup> and in saline solutions of proteins.<sup>7</sup> It thus seems likely that all of the free progesterone in this, as in previous studies,<sup>21</sup> was transported in the blood in simple solution. Brewer,<sup>8</sup> on the basis of histological studies, concluded that the functional activity of the corpus luteum of menstruation increases gradually during the first eight to ten days of its life and that thereafter there is a decline in activity. This conclusion appears to be well supported by the progesterone curves of the present study, particularly if allowance is made for the possibility that blood samples may not always have been drawn when the plasma progesterone was at its peak.

There is no apparent correlation between the onset of menstruation and the plasma progesterone level. However, it is quite clear that in all of the four donors studied there were instances when the menses began and continued for 24 hours or longer although appreciable quantities of free progesterone were still circulating.



The relatively high waking temperature during the luteal phase of the human menstrual cycle has repeatedly been observed.<sup>3, 4, 11, 12, 13, 17, 23, 24</sup> Indeed, while injection of estrogens does not elevate waking or basal temperatures, administration of progesterone is followed by a conspicuous temperature elevation in normal, amenorrheic, postmenopausal, and castrate women and in men.<sup>1, 5, 9, 25</sup> The close coincidence in the present study of the progesterone curves and the elevated temperature curves is quite in keeping with previous observations, but this relationship does not explain the irregular temperature elevations seen in the absence of detectable amounts of progesterone in H3 (Jan.).

The term "bound progesterone" has been used with some reservation, since the binding of progesterone to protein, while it appears likely, is not proved. This point has been discussed in an earlier paper.<sup>21</sup> The physiological inactivity of bound plasma progesterone in mice, even in relatively high concentrations of the substance, has previously been demonstrated.<sup>22</sup> In the present experiment, as in previous studies,<sup>16, 20, 21</sup> under physiological conditions the concentration of the bound progesterone has invariably been relatively low (0.5  $\mu\text{g}$  or less per cubic centimeter plasma). Although the bound fraction may in man, as it does in the mouse,<sup>16</sup> testify to the important function of hepatic inactivation, it does not at present appear that this fraction plays a significant role in the menstrual cycle.

### Summary

Systemic plasma progesterone levels were determined by bio-assay of blood samples drawn at frequent intervals for about six weeks from each of four young women. Waking temperatures were recorded daily during the same periods. Free progesterone appeared a day or two before, or coincidental with, a major rise in waking temperature and, in two instances, a few hours before Mittelschmerz. The level of the hormone rose to peaks of 1.7 to 5.2  $\mu\text{g}$  per cubic centimeter plasma and then declined, although in most cases the progesterone did not disappear until after the onset of the menses. The rise and fall of progesterone levels and waking temperatures in a given menstrual cycle agreed rather closely. Sample assays for bound progesterone showed the concentrations of this fraction always to be relatively low, usually so low as to be undetectable.

The author is particularly indebted to Dr. A. W. Makepeace for several important suggestions and to Drs. Makepeace, S. L. Palay, H. Tuchmann-Duplessis, and J. T. Wolstenholme for drawing blood samples. Finally, the work would have been impossible without the generous and friendly cooperation of the donors and the excellent technical assistance of Miss A. Jayne Foley.

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## GENITOURINARY CHANGES FOLLOWING GYNECOLOGIC SURGERY\*

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THE female pelvic organs are in such close proximity to the lower urinary tract that pathological changes in the pelvic viscera are often reflected in urinary symptomatology. Urinary complaints are relatively frequent in the gynecological patient. Whether they are due to pressure from a pelvic mass, or infection, or distortion in the pelvic anatomy by benign or malignant new growths, or changes in position of the uterus with its appendages, nevertheless, the complaints are frequently primary for the patient. These complaints urge the patient to seek relief from her gynecologic disease. That women with prolapse and cystocele may have distortion of the urinary tract was shown in 1923 by Brettauer and Rubin,<sup>1</sup> who found hydronephrosis and hydroureter in the majority of them. They believed that the ureteral dilatation was due more to pressure from the angulated uterine arteries as they crossed over the lower ends of the ureter than to the pressure caused by herniation through the genital canal. Others<sup>2, 3</sup> have shown upper urinary dilatation with prolapse of the uterus, but the percentage of incidence is by no means uniform. In a more recent study by Everett and Sturgis,<sup>4</sup> in 100 patients with various gynecological diseased conditions, it was found that about 50 per cent of the patients had either unilateral or bilateral dilatation of the upper urinary tract. In a series by Kretschmer and Kanter,<sup>3</sup> which included mostly uterine tumors with some ovarian cysts, the incidence of upper urinary tract dilatation varied from 54 per cent to 81.9 per cent and, following appropriate surgical procedures, the return to normalcy was present in 72.5 per cent of the patients. In Everett's series, in a postoperative follow-up of thirty cases, over 43 per cent of patients had a complete return to normal; 30 per cent had partial regression of the diseased condition and over 26 per cent showed no change in the urinary tracts. The relative difference in the percentages of cases in which the urinary tract returned to normal in the two reports above mentioned is accounted for by the latter authors by inclusion of cases of pelvic inflammatory disease, in which cases the distortion of the lower ureter with the local inflammatory condition prevented full recovery. Of course, when a pelvic mass which was not associated with any inflammatory reaction in the surrounding tissue was removed, a greater recovery rate of the local ureteric pressure reaction was anticipated, unless prolonged pressure caused organic changes in the wall of the ureter, either by angulation of the uterine vessels or pressure of the tumor extrinsic

\*Aided by a grant from the Kate Lubin Research Foundation, Inc.

to the ureter with resulting dilatation of the ureters and possibly the kidneys above the point of disturbance.

Since in over 50 per cent of the cases, according to one report, there was persistence of dilatation of the upper urinary tracts following the proper gynecological surgery, it apparently indicates the need for careful study of the genitourinary tracts in all patients with various gynecologic conditions. This is done to prevent future serious organic disease of the kidneys.



Fig. 1.

Fig. 1 (Case 18).—Preoperative pyelogram and cystogram showing atonicity of bladder and dilatation of ureters.



Fig. 2.

Fig. 2 (Case 15).—Preoperative cystogram reveals distortion of bladder contour with marked atonicity.

### Material

Bladder symptoms and other urinary complaints seem to play an important part in our gynecological histories and we look for the alleviation of these complaints following therapy, whether it be medical or surgical. It was decided, therefore, to observe a series of gynecological patients who were to undergo operative procedures at the Cumberland Hospital. This study was undertaken jointly by the Department of Obstetrics and Gynecology and the Department of Urology. We selected no special cases but routine operative cases admitted to our wards and the following studies were performed: twenty-four to forty-eight hours preoperatively, each patient had a cystoscopic examination and cystometric studies were performed, followed by retrograde pyelography and cystograms. About two weeks postoperatively, the same procedure was repeated. In our first seven cases, we carried out a three-month follow-up restudy of the urinary tract, in which group only minimal changes were noted as compared to



the two-week follow-up x-ray study. In our series, we examined 24 cases in all extending from February to July of 1948. The pathological conditions included nine cases of fibromyomas of the uterus, three with premenopausal bleeding, two with cystoectoceles, two with third-degree prolapse of the uterus, one with prolapse of the cervical stump, one with bilateral dermoid cysts of the ovary, one with adenoma malignum of the uterus, four with chronic tubo-ovarian disease, and one with a left ovarian cyst.



Fig. 3 (Case 15).—Preoperative pyeloureterogram shows dilatation of upper urinary tract with distortion of ureters.

### Comment

Tumors of the uterus should perhaps first be investigated relative to pressure effects upon the lower urinary tract with their associated bladder distortion. Such studies would perhaps indicate that surgery is a satisfactory approach toward the alleviation of the patient's urinary symptoms. It really becomes a primary indication for surgery when urinary tract symptoms are pronounced because, even if the symptoms of a fibroid growth in the uterus, whether they be menorrhagic or menometrorrhagic, are alleviated, nevertheless, the pressure effects are not ameliorated and further functional disturbances finally progress to organic changes in the lower urinary system. By the same token, chronic pelvic inflammatory disease, with its associated distortion of the ureters and bladder, treated conservatively, may serve only to delay alleviation of the functional disturbances in the urinary tract. Perhaps all tumors of the uterus and all cases of pelvic inflammatory disease should have genitourinary

studies. Even if the gynecologic symptoms are relatively mild, nevertheless, the possibility of future changes in the urinary tract should be considered. If the already existing diseased condition has caused alterations in the genitourinary tract, surgery should be given serious consideration.

In several reports that have appeared in the literature, the changes in the urinary tract occasioned by gynecologic disturbances have been indicated. Both the preoperative and postoperative studies have shown that not more than 50 per cent of the disturbances in the urinary tract are improved by the appropriate operative procedure to correct the gynecologic pathology. In our study, we have gone one step further and not only performed x-ray and cystoscopic visualization of the genitourinary system, but have included cystometric studies in all of the cases, attempting to discover changes in tonus in this organ in its relationship to the remainder of the genitourinary tract. In addition, the effects of the surgical treatment of the diseased condition upon the tonicity of the bladder were observed.

### Summary

There were ten cases of fibromyomas of the uterus, the fibroids varying in size up to that of four to five months' gestation. In most cases, there was bladder distortion preoperatively, which improved postoperatively. While in several cases the ureters were displaced laterally as they entered the bladder, nevertheless, in only two cases was there evidence of hydronephrosis, which improved in both cases following surgery.

In the five cases of uterine displacement, all showed evidence of bladder atonicity and in one case of third-degree prolapse of the uterus there was dilatation of the upper urinary tract. Postoperatively, there was residual atonicity of some degree. In nearly all the cases, the tone was moderately improved.

In three cases of chronic pelvic inflammatory disease, hydronephrosis was evident in two cases and displacement of the ureters in the third case. Postoperatively, the two patients with hydronephrosis were improved and one was restored to normal condition. In the third case, where the ureters were displaced laterally, the position of the ureters returned to normal postoperatively.

In the three cases of menopausal bleeding, there was one case of an atonic bladder and one with a hypertonic bladder. Both of these were restored to normal postoperatively.

In one case of ovarian cyst, a displaced ureter was returned to normal position postoperatively, and in one case of bilateral dermoid ovarian cysts, the atonic bladder was improved in tonus postoperatively.

In one case of carcinoma of the fundus, an atonic bladder was present both preoperatively and postoperatively.

### Conclusions

1. The cystograms and pyelograms, in a majority of instances, revealed a correction of the deformity or distortion produced either by pressure from the adjacent mass or by distortion associated with chronic pelvic disease.

2. Cystometric examination, as well as the cystograms, revealed a persistence of loss of bladder tonus.

3. The loss of bladder tonus may account for the persistence of bladder symptoms after the pressure on the bladder or ureters has been relieved.

We wish to extend our gratitude for the cooperation of Dr. H. Koiriansky, Director of the Department of Radiology, Cumberland Hospital.

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## PUERPERAL INVOLUTION OF THE URINARY TRACT

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**C**RUVEILHIER, in 1841, noted dilation and hypertrophy of the urinary tract at postmortem examination in pregnant women. Subsequently, many authors, including Crabtree, Duncan and Seng, Baird, and Mengert and Lee agreed that the right side dilates in practically every pregnant woman, and the left side in about three-fourths of them. Furthermore, there is general agreement that, although dilation occurs earlier in the parous than in the primigravid woman, it is usually more marked in the latter. There is, however, little agreement as to when the urinary tract returns to its nonpregnant state and for that reason this study was undertaken.

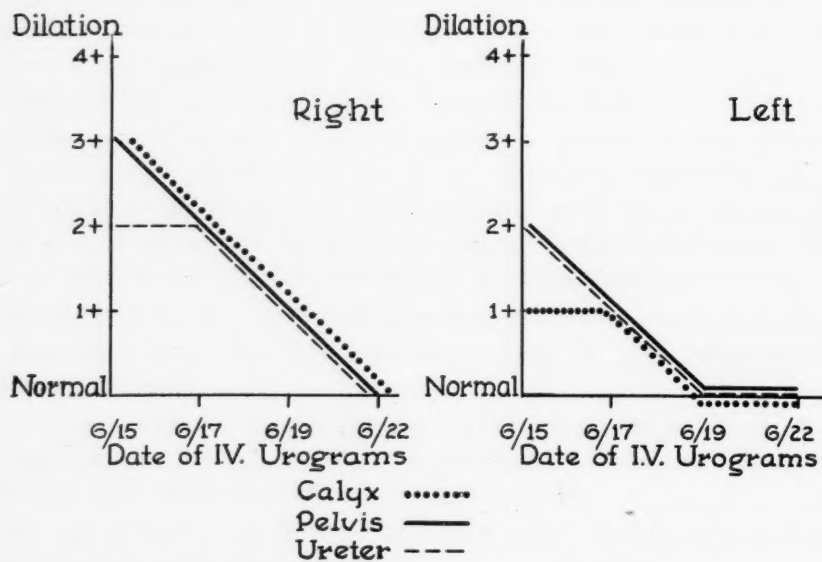


Fig. 1.—Graphic representation of return to normal in patient V. R., who is typical of average. The degree of dilation was arbitrarily graded with 4 as maximum. Note that the right-sided return to normal from a maximum of 3 plus was consummated within seven days.

Fig. 2.—Excretory urogram, made three days before delivery. Urinary tract dilation was graded as follows:

Right, calyx  $2\frac{1}{2}$ , pelvis 3, ureter 3.

Left, calyx 2, pelvis 2, ureter  $2\frac{1}{2}$ .

Fig. 3.—Two days post partum. Note that the urinary tract is almost normal.

Fig. 4.—Five days post partum.

Fig. 5.—Thirty-four days post partum.



Fig. 2.



Fig. 3.

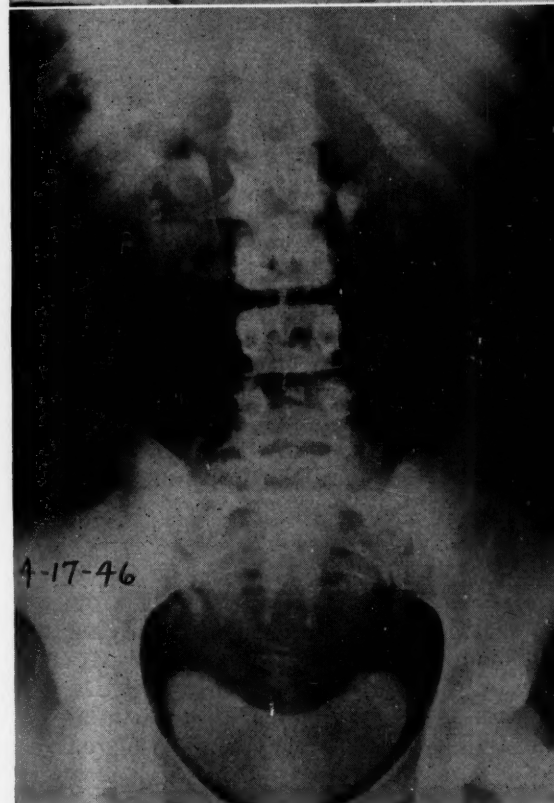
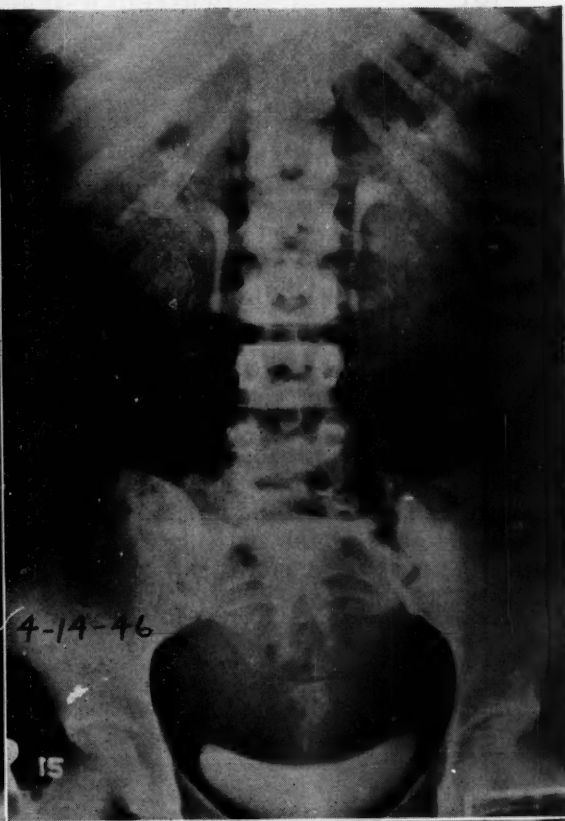


Fig. 4.

(For legends, see opposite page.)

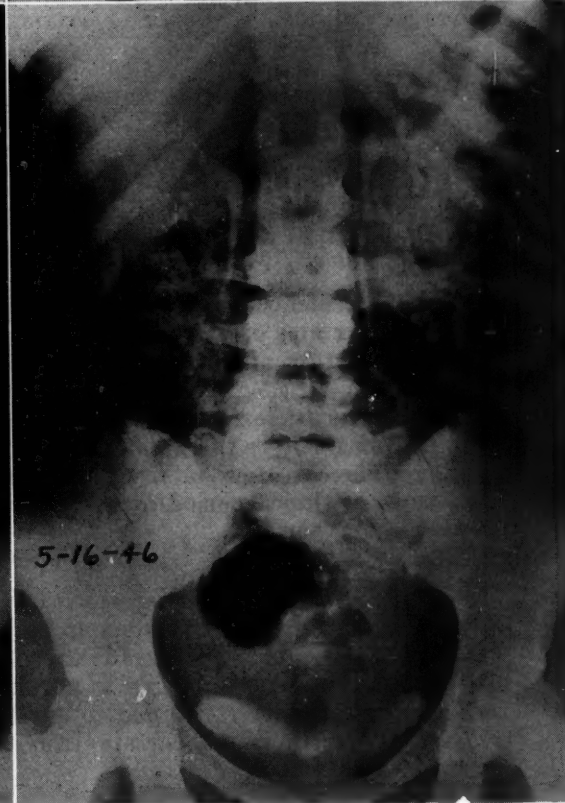


Fig. 5.

### Methods

Twenty-three normally pregnant women chosen only for convenience were used in this study. Eight were primigravid. An initial excretory\* urogram was made prior to labor or during early labor. Subsequent urograms were made two, four, and seven days post partum, or as close to this schedule as possible. Films were exposed five, fifteen, and twenty minutes after injection of the dye and best results were generally obtained with the twenty-minute picture. It should be noted, in passing, that our customary obstetric management includes early ambulation.

### Results

The time of completed involution of the right and left calyx, pelvis, and ureter was arbitrarily judged after study of all the films, and is tabulated in Table I. It is readily apparent that the right side of the urinary tract was completely involuted by the seventh puerperal day in more than three-fourths of the patients. On the left side involution was even more complete, since nearly nine-tenths of the patients exhibited no roentgenologic evidence of dilation at this time. Also, more than half of the twenty-three women returned to normal within four days.

TABLE I. COMPLETED INVOLUTION OF THE PARTS OF THE URINARY TRACT EXPRESSED IN NUMBERS OF PATIENTS ADJUDGED NORMAL ON THE SECOND, FOURTH, AND SEVENTH PUERPERAL DAY AS EVIDENCED BY EXCRETORY UROGRAMS  
(THERE WERE 23 PATIENTS IN THE ENTIRE SERIES)

DAYS POST PARTUM	NUMBER OF PATIENTS WITH COMPLETED INVOLUTION					
	RIGHT			LEFT*		
	CALYX	PELVIS	URETER	CALYX	PELVIS	URETER
2	6	2	2	4	4	0
4	14	12	12	18	13	13
7	20	19	19	21	18	20

\*Based on 22 patients, since one exhibited no leftsided dilation.

In order to illustrate the rate of involution, each part of each side of the urinary tract was arbitrarily graded on the basis of 4 representing maximum. Fig. 1 depicts the results of such grading in a patient, V. R., who is typical of the average.

Visual evidence of puerperal involution of the urinary tract is afforded by roentgenograms of a typical patient, T. P. H. The films were exposed three days ante partum and two, five, and thirty-four days post partum (Figs. 2-5). Ante partum her degree of dilation was graded as follows: right, calyx  $2\frac{1}{2}$ , pelvis 3, ureter 3; left, calyx 2, pelvis 2, ureter  $2\frac{1}{2}$ . It is obvious that involution took place before the first puerperal film was made, two days after delivery, and that there are few, if any, apparent differences among the four puerperal films, representing a period of thirty-four days.

### Discussion

The period of time during which involution of the urinary tract occurs after delivery is usually quoted as six to eight weeks. Duncan and Seng, studying postpartum patients by retrograde urograms made between the ninth and twenty-fifth days, noted a rapid return to normal in only the minority of their patients, and felt the majority continued to exhibit right, left, or bilateral ureteral dilation. However, it is not certain from the article whether they made isolated

\*Diodrast was used in this study.

observations on individual patients or followed a single patient through to completed involution. Retrograde pyelography, the method they employed, does not lend itself to repeated observation. Kretschmer and others felt that about 60 per cent of their patients returned to normal by the end of two weeks. On the contrary, Mengert and Lee found that there was often marked reduction in size within six to twenty-four hours puerperally, and in twelve normal patients observed completed involution of the urinary system by the ninth to eleventh day. Furthermore, they felt that the majority of their forty-one patients showed marked reduction in the caliber of the urinary system by the end of the twelfth postpartum day.

Traut and McLane, employing a Trather hydrophorograph, showed a marked return of muscular irritability of the urinary tract during the last month of pregnancy. Perhaps there is prompt puerperal constriction, followed after some days by a secondary relaxation. With one exception (T. P. H., Figs. 2-5) our patients were followed for only seven days. It is known that pelvic infection, not necessarily of the urinary tract, will delay involution or produce recurrence of dilation. Mengert and Lee reported five patients with febrile puerperiums who experienced sluggish and delayed involution. One of their patients with early, rapid, and almost complete involution developed a postpartum infection and immediately exhibited a recrudescence of dilation. Crabtree reports that often, with postpartum infection, involution is delayed and that most infected patients approach normal kidney and ureteral conformation at about four months. We also found delayed involution in patients with puerperal infection.

### Conclusions

1. There is either a return to normal size, or a marked reduction in caliber of the upper urinary tract of the normal puerperal woman within a week after delivery.
2. Involution is delayed or dilation may recur in the infected patient.

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## HUMAN SERUM ALBUMIN IN THE TREATMENT OF ECLAMPTOGENIC TOXEMIA\*†

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THE variation in concentration of plasma protein during pregnancy has presented a problem to investigators for many years. This has been particularly true to those who are searching for the possible relationship of plasma protein values to the etiology of eclamptogenic toxemia. Plass and Mathews<sup>1</sup> in 1926 presented observations on the level of the plasma protein fractions in a series of patients throughout gestation. Since that time other reports<sup>2</sup> have appeared which confirm earlier studies. In brief, these changes show a progressive decrease in the concentration of total plasma proteins, particularly the albumin fraction, during the course of normal pregnancy.

Associated with the changes in albumin concentration are those in plasma volume, extracellular fluid, and red-cell mass.<sup>3, 4</sup> During normal gestation, the plasma volume increases until the last six weeks of pregnancy when it begins to decrease from the maximum level attained. The extracellular fluid volume on the other hand increases up to the onset of labor. This increase is most marked during the last ten weeks of pregnancy. In unpublished studies it has been found that the total circulating red-cell mass does not decrease but there is actually a definite increase during pregnancy.

Observations in eclamptogenic toxemia show an actual decrease in total circulating protein as compared with that in normal pregnancies. The associated changes show an increase in plasma volume equal to or less than that occurring in normal pregnancy. The extracellular fluid volume shows an increase greater than that occurring in normal gestation.<sup>5</sup> This would indicate that, in eclamptogenic toxemia, there may be an alteration in the normal ratio of the volume of fluid inside and outside the vascular system. The results of studies made of the total red-cell mass in eclamptogenic toxemia have never been reported.

Many substances have been used in an attempt to correct the hypoproteinemias of eclamptogenic toxemia. Among these may be mentioned amino acids and protein hydrolysate<sup>6</sup> and concentrated plasma.<sup>7</sup> The results of these studies

\*Supported in part by a grant from the Charles H. Hood Foundation.

†The serum albumin used in this study was processed by the American National Red Cross from blood which it collected from voluntary donors. This is one of a series of investigations on serum albumin being carried out with material supplied by the American National Red Cross. As soon as sufficient data become available to justify final conclusions concerning its therapeutic value, a full report on the use of serum albumin in medical practice will be published by the Committee on Blood and Blood Derivatives of the Advisory Board on Health Services of the American National Red Cross.



indicate that protein therapy is a valuable adjunct in the treatment of eclamptogenic toxemia. Definitive treatment, however, is still the object of investigation.

During the last two years at the Boston Lying-in Hospital, patients with eclamptogenic toxemia have been treated using large amounts of concentrated human serum albumin. Table I indicates the pertinent clinical and laboratory findings in six of these patients who were given amounts of albumin varying from 75 to 250 Gm. intravenously.

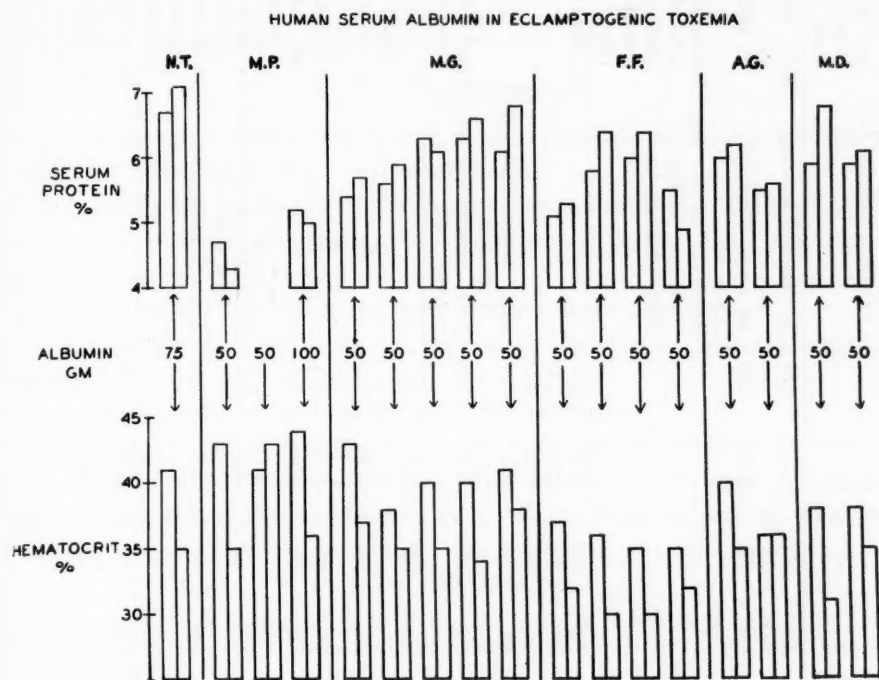


Fig. 1.

### Comment

One can readily see that there is no continuity in the response of these patients to intravenous albumin. Human serum albumin can be given to the eclamptogenic toxemic patient with minimal danger of pulmonary edema or renal failure. With the administration of 50 Gm. of albumin over periods ranging from seventeen minutes to four hours, there was no persistent rise in systolic blood pressure, evidence of pulmonary râles, nor evidence of suppression of urine output. The most consistent finding following albumin therapy in these patients was the fall in large vein hematocrit (Fig. 1). Although this is not an indication of change in total body hematocrit, transient hemodilution may be assumed to have occurred since only a slight rise in serum protein concentration was generally seen. A further indication of the transient increase in plasma volume was seen in a temporary diuresis during and following albumin therapy.

The results obtained using salt-poor human serum albumin were unsatisfactory in several respects. Hypertension was not relieved. It was hoped that by increasing the plasma volume, the vascular tree would become more completely filled with blood, thus allowing for compensatory vascular dilatation.

TABLE I

PATIENT	AGE	PARITY	ALBUMIN GIVEN (GM.)	BLOOD PRESSURE*		HEMATOCRIT %		SERUM PROTEIN %*		OTHER MEDICATION	REMARKS
				1	2	1	2	1	2		
N. T.	22	1	75	140/100	130/90	41	35	6.7	7.1	10% Glucose i.v. mag- nesium sulfate, i.m.	Convulsions before therapy, 1400 c.c. urine in 5 hours following albumin. Bag induction; ver- sion; delivered stillborn.
M. P.	27	1	50 50 100	155/108 150/120 178/114	134/98 175/120 168/116	43 41 44	35 33 36	4.7 5.2	4.3 5.0	50 units Vertavis, p.o. 40 units Vertavis, per os	Mild headache; minimal edema; 4+ albuminuria.
M. G.	23	1	50 50 50 50 50	176/112 178/115 194/120 190/126 160/110	176/112 178/112 160/100 154/90 140/90	43 38 40 40 41	37 35 35 34 38	5.4 5.6 6.3 6.3 6.1	5.7 5.9 6.1 6.6 6.8	20% mag- Eclamptic convulsion 5 hours after albumin therapy. Pitocin stim- ulation of labor; Voorhees bag; internal version. Delivered 2 pound, 8 ounces stillborn	3+ albuminuria
F. F.	20	1	50 50 50 50	150/100 140/100 136/96 142/100	145/100 114/90 120/76 132/96	37 36 35 35	32 30 30 32	5.1 5.8 6.0 5.5	5.3 6.4 6.4 5.4	25% magnesium sul- fate, i.m. 25% magnesium sul- fate, i.m.	47 pound weight gain; 2+ albu- minuria. 14 pound weight loss; 4+ albu- minuria. Chill following infusion; induction of labor. Delivered 5 pound, 2 ounces, active infant.
A. G.	22	1	50 50	144/116 160/118	140/90 144/96	40 36	35 36	6.0 5.5	6.2 5.6	25% magnesium sul- fate, i.m. Normal saline, i.v.	Chill following infusion. 1+ albuminuria; fetal heartbeat dis- appeared. Spontaneous delivery, nonviable fetus.
M. D.	21	1	50 50	134/86 142/90	150/100 148/100	38 38	31 35	5.9 5.9	6.8 6.1		40 pound weight gain; 3+ albu- minuria. Induction of labor; delivered 5 pound, 4 ounce active infant.

\*1. Values before albumin.  
2. Values after albumin.

Second, the increase in urinary output following albumin therapy was fleeting. No effective diuresis was obtained until either intrauterine death had occurred or delivery had been effected. (It may be of interest that urinary albumin determination in one patient showed a marked increase in the amount of albumin excreted during treatment. This may be a limiting factor in achieving desirable results.)

Last, only two of the six eclamptogenic toxemia patients obtained viable infants, and these two were the least severely ill mothers. Of the four mothers who lost their infants, two had spontaneous intrauterine death on the fourth and eighth hospital days with subsequent improvement of their illness. The remaining two mothers lost their extremely premature infants as a direct result of the obstetrical method elected to terminate their pregnancies.

### Summary

1. Observations are presented on six patients with eclamptogenic toxemia receiving salt-poor human serum albumin.

2. Salt-poor human serum albumin was administered intravenously in doses of 50 Gm., with total amounts varying from 75 to 250 Gm. over periods of five hours to eleven days.

3. Transient hemodilution and diuresis were produced.

4. In these six patients, no pulmonary edema or urinary suppression was observed.

5. Hypertension and edema were unchanged.

6. The patients' courses were not appreciably affected by this treatment. Two viable infants were obtained. Two infants underwent spontaneous intrauterine death and the remaining two infants died following obstetrical intervention.

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## THE ROLE OF FLUIDS IN RELIEVING BREAST ENGORGEMENT WITHOUT THE USE OF HORMONES\*

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**B**EFORE the use of hormones, the relief of breast engorgement was accomplished by dehydration, the use of saline cathartics and analgesics, and the application of breast binders. Later, the androgens and estrogens became very popular for this purpose almost to the complete sacrifice of the former routine.<sup>1</sup> Then certain observers began to notice disadvantages of the use of hormones:

1. The androgens were too expensive and some of the investigators feared a permanent androgenic effect.
2. Following the use of estrogens, there was a return of breast engorgement in many cases after the patient was discharged from the hospital.<sup>2, 3</sup>
3. Bloom<sup>3</sup> stated that 30 per cent had a delay in menstruation post partum for as long as two months past the expected time.
4. Rutherford<sup>4</sup> warned against the long-continued use of either estrogen or androgen because of the deleterious effects upon the regeneration of uterine mucosa post partum.
5. Occasionally there was profuse bleeding the fourth or fifth week post partum, at times necessitating transfusion and curettage. The specimens so obtained usually showed endometrial hyperplasia.
6. Hamblen<sup>5</sup> stated that there was no need or rationale for endocrine therapy of breast engorgement and that it might complicate puerperal recovery of normal cyclic ovarian function.

With all the accumulated evidence against the use of hormones for the relief of breast engorgement, some obstetricians discarded them in favor of the older routine of dehydration as popularized by De Lee.

A question then arose as to the advisability of employing dehydration in the case of a nonnursing morbid puerpera who was receiving sulfadiazine. The alternatives were to switch to penicillin, to use stilbestrol, or force fluids with the sulfonamide and observe what happened to the engorging breasts. The last plan was selected in our study. The results were so gratifying that it was decided to investigate what role fluids played in the drying up of the breasts in a series of postpartum patients.

### Material

A total of 278 patients, divided into three groups, were used in this experiment. Group "F" (forced fluids) included 139 patients in each of whom the intake of fluids was from 2,500 to 5,000 c.c. daily. Group "R" (restricted fluids) had 89 patients for whom fluids were restricted to less than 1,500 c.c.

\*Presented at a meeting of the Brooklyn Gynecological Society, October 19, 1949.



daily, and who received magnesium sulfate by mouth on the third day when the breasts were full. Finally, in group "C" there accumulated 50 patients who failed to force fluids satisfactorily but took them freely. Their intake varied from 1,500 to 2,500 c.c. daily and they were therefore called the control group.

The method employed by the authors to dry up the breasts was as follows:

1. Fluids were given as indicated above.  
2. In all cases a well-fitted maternity brassiere was advised instead of a tight breast binder in order to accomplish support without compression. In some instances a binder was employed.

3. No saline cathartics or purges of any kind were given, except in group "R."

4. Medication in the form of codeine 0.032 Gm. in combination with aspirin 0.65 Gm. was given to the patient when and if the breasts became painful.

5. No patient was included in this series who nursed her baby or pumped her breasts at any time during this study. It was desired to avoid the suckling stimulus which would increase the engorgement of the breast.

6. Daily records were kept, which included the name of the patient, days post partum, condition of the breasts, medication required, and daily intake and output of fluids.

Objectively the breasts were classified as "soft," "filling," "full," "hard," or "hard, red, and tender." The amount of medication required for the relief of breast discomfort was used as an index of severity of subjective complaints.

### Results

The objective findings, chiefly the condition of the breasts, were similar in the three groups (Tables I, II, and III).

TABLE I. FORCED FLUIDS, 139 PATIENTS\*

DAYS POST PARTUM	1	2	3	4	5	6	7	8
Hard, red and tender			3	4	1			
Hard			7	9	11	4		
Full			19	70	36	17	4	
Filling		21	79	40	63	33	10	1
Soft	139	118	31	16	28	69	42	9

\*There is a discrepancy between the total number of patients and the breasts qualified from the 6th day on because some patients were discharged from the hospital as early as the 6th day.

TABLE II. CONTROL GROUP, 50 PATIENTS\*

DAYS POST PARTUM	1	2	3	4	5	6	7	8
Hard, red, and tender			3	2				
Hard		1	1	11	7			
Full		1	11	21	17	11		
Filling		4	23	9	16	16	5	1
Soft	50	44	12	7	10	18	12	6

\*See note on Table I.

TABLE III. RESTRICTED FLUIDS, 89 PATIENTS\*

DAYS POST PARTUM	1	2	3	4	5	6	7	8
Hard, red, and tender			2	6	4	2		
Hard		1	7	15	11	1		
Full		3	27	45	29	19	4	2
Filling	1	20	36	12	36	24	6	
Soft	88	65	17	11	9	34	37	8

\*See note on Table I.

An analysis of results in the three groups yielded the following significant observations (Table IV):

TABLE IV

	MEDICATION		HARD (ENGORGED)		RED, TENDER		FEVER	
	NO.	%	NO.	%	NO.	%	NO.	%
Forced fluids	60	43	26	19	4	3	4	3
Control fluids	21	42	11	22	3	6	1	2
Restricted fluids	37	42	16	18	6	7	5	6
No. of patients in forced fluids group					139			
No. of patients in control fluids group					50			
No. of patients in restricted fluids group					89			
Total patients					278			

1. There was a percentage of hard breasts in the three groups, i.e., 19, 18, and 22 per cent each in groups "F," "R," and "C," respectively.

2. In each category a few patients exhibited hard, painful, tender, reddened breasts almost simulating a true mastitis. The percentage was lowest in group "F" namely 3 per cent as contrasted with 7 per cent in group "R," and 6 per cent in group "C."

3. There were several patients in each group who developed a low-grade fever on the third or fourth day post partum. This was accompanied by hardness and tenderness of the breasts and no other apparent cause for the fever was noted. They were therefore classified as "breast fever." In this category groups "C" and "F" accounted for 2 per cent and 3 per cent, respectively, as compared with 6 per cent for group "R."

4. Regarding medication required for the relief of pain, there was a similarity among the three groups, 43 per cent, 42 per cent, and 42 per cent. In group "F," analgesics were given to 60 patients 117 times for an average of 1.95 doses per patient. In the control group, 34 doses were given to 21 patients, or 1.62 per patient, and in group "R" 60 times to 37 patients for 1.62 doses per patient.

5. The average daily output was 2,300 c.c. in group "F," 1,500 c.c. in group "C," and 1,160 c.c. in group "R" (Table V).

TABLE V.

	AVERAGE DAILY INTAKE	AVERAGE DAILY OUTPUT
Group "F" Forced fluids	2,500-5,000 c.c.	2,300 c.c.
Group "R" Restricted fluids	Less than 1,500 c.c.	1,160 c.c.
Group "C" Control fluids	1,500-2,500 c.c.	1,500 c.c.

6. Parity seemed to play no part in this study. There were 36 per cent primiparas in group "F," 28 per cent in group "C," and 43 per cent in group "R." The multiparas totaled 64 per cent, 72 per cent, and 57 per cent, respectively.

7. The method of delivery was not included in this study for it is felt that it has little bearing on the problem.

#### Comment

According to Zondek,<sup>7</sup> the high level of estrone and progesterone in the blood during pregnancy prepares the pituitary for the secretion of prolactin

which in turn causes the breasts to fill with milk. The stimulus for its secretion is given by the sudden withdrawal of estrone and progesterone from the body at birth.

The maintenance and control of lactation, as pointed out by Hamblen,<sup>5</sup> are attributed generally to a nervous stimulation of the lactogenic function of the pituitary by the suckling reflex.

If the engorged breast is not stimulated by nursing, the formation of milk gradually and automatically ceases. The engorgement is said to be caused not by the milk itself but by venous and lymphatic stasis.<sup>8</sup> Therefore, unless dehydration were so extreme as to create a physiological imbalance of the endocrine as well as vascular system, it should not be effective in relieving engorgement of the breast. In the same manner, a physiologically normal puerpera should be able to handle any excess of fluids by mouth by merely excreting more urine. Thus, forcing of fluids should not increase the secretion of prolactin with consequent breast engorgement. Along these lines, Gurdjian<sup>9</sup> has shown that contrary to popular opinion the forcing of fluids in cases of acute injury to the head does not cause increase in the cerebrospinal pressure, in the majority of instances. Cannon<sup>10</sup> states that it is apparently difficult to upset coordinated physiological functions maintaining the constancy of the organism. Lubin<sup>3</sup> and Walsh and Stromme<sup>6</sup> in their series did not restrict fluids but did not state the amounts consumed. Regardless of the mechanism involved, the results of this study seem to indicate that fluids play little if any physiological part in the drying up of the breasts in the nonnursing woman. From the practical standpoint, however, it would seem to make a great difference. She is much more content when she can eat and drink what she likes and not be disturbed by the use of cathartics.

### Summary and Conclusions

The influence of the variations in the amount of fluid ingested on drying up the breasts, without the use of hormones, was investigated in a series of 278 postpartum nonnursing mothers. The results indicate that the forcing of fluids is no less effective in drying up the breasts than is the "dehydration" method. In addition the regimen offers several distinct advantages:

1. Patients are very uncomfortable when they restrict fluids, particularly in the summertime.
2. It avoids the necessity for saline cathartics which are very unpleasant to the sore perineum.
3. The patients develop a sense of well-being and enthusiasm when they learn they can eat and drink freely though they are drying up their breasts.
4. The physician has the opportunity of forcing fluids whenever indicated by the condition of the patient and especially during the administration of sulfonamides.

Although some obstetricians strongly favor the hormonal routine for the relief of engorgement of the breasts, it is hoped that they will be willing to try this method of forcing fluids since the advantages are many and the objections so few.

Since the authors' series of cases is admittedly small, it is hoped that others will investigate the problem.

Appreciation is expressed to the Misses Mollett, Rarick, Carle, Pierce, and Roberts, Nursing Supervisors, who were responsible for many of the observations made in this study.

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## THE USE OF PROSTIGMIN IN HEARTBURN OF PREGNANCY

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IN ITS present-day approach, prenatal care embraces not only those steps essential to the ultimate safety of mother and child but extends even into the field of painless childbirth, as represented by the theories of Grantly Dick Read. This concept takes cognizance of a number of symptom complexes and clinical syndromes, the alleviation of which contributes to the safety of both mother and child and also lessens the discomfort of the physiological changes inherent to pregnancy. The heartburn of pregnancy belongs in this category. The nagging persistence of this complaint interferes with proper diet, deprives the patient of needed rest, and destroys her sense of well-being. It is in most cases easily and quickly, although temporarily, relieved by bicarbonate of soda. It is this very fact which makes its proper control by other measures essential, for increased sodium intake from bicarbonate therapy tends to augment the already positive water balance of normal pregnancy with a resultant predisposition to excessive weight gain, longer labors, and pre-eclampsia.

For the purpose of this study, heartburn is defined as a burning or scalding sensation, localized beneath the sternum in the region of the xiphoid process. It is reported to be a disturbing factor in two-thirds of all pregnancies,<sup>1</sup> and is more intense in the last trimester. Sixty per cent of cases first appear in the first two trimesters and forty per cent occur from six weeks before term to term.

Gastric hyperacidity was accepted for a long time as the causative factor in the production of this syndrome, until it was shown by Jones and Richardson<sup>2, 3</sup> to be due to a neuromuscular phenomenon. By applying pressure to various areas within the esophagus by means of a distended balloon there was gained evidence that the symptom is due to spasm of the cardiac sphincter. This was confirmed by the observation that the same sensation could be reproduced by pouring bland liquids at room temperature into the same sites and thus achieving a similar type and degree of distention. Waves of reverse peristalsis were apparent while the sensation persisted.

Changes in the gastrointestinal tract during pregnancy include those of position, secretion, motility, and tone. Hansen<sup>4</sup> plainly depicted the anatomical distortion of the stomach in advancing pregnancy and Williams<sup>1</sup> corroborated these findings by means of various studies. The enlarging uterus was shown to encroach upon the abdominal organs, forcing the normally vertical stomach out of position. As a result, the gastric fundus lies under the left leaf of the diaphragm, the greater curvature lies near the cardia, and the entire organ is rotated 45 degrees to the right. Strauss and Castle;<sup>5, 6</sup> as well as others,<sup>7, 8, 9</sup>

have effectively demonstrated that 75 per cent of pregnant patients do not secrete normal amounts of hydrochloric acid or pepsin during more than half the period of gestation, although Labate<sup>10</sup> points out that there is an improvement in secretion during the last trimester. In any event, unlike the constancy in the nonpregnant, wide variations in the amount of gastric secretion occur during pregnancy, mostly tending toward diminution. Concomitant with diminished gastric secretion are loss of tone and diminished motility. With the normal emptying time of the stomach considered to be about two hours,<sup>11</sup> the increase in pregnancy may amount to 100 per cent, progressing to the onset of labor when there is practically no motility or tone, with a free reflux of duodenal contents. Such changes are sufficient to bring about distention of the lower esophagus, with the consequent production of heartburn.

There seems little doubt that there exists a fundamental relationship between the autonomic nervous system and the endocrine glands and accordingly it seems not unreasonable to suppose that the profound hormonal changes in pregnancy may, through an influence on the abdominal branches of the vagus, bring about the altered gastrointestinal changes described. However, the exact mechanism of the hormonal effect of pregnancy on the gastrointestinal tract is not known. It is probably a combination of direct and indirect factors acting through the autonomic nervous system: through changes in electrolytic balance peculiar to pregnancy<sup>12</sup>; and through certain phases of vitamin B complex metabolism. Likewise, the mechanism by which Prostigmin relieves heartburn, as will be described below, can only be postulated. Certainly, part of the effect, at least, must be through stimulation of parasympathetic activity. It will be recalled that the drug has the property of inhibiting the action of cholinesterase, and thus increasing the available acetylcholine. This, in turn, by permitting freer transmission of nerve impulses across parasympathetic nerve endings innervating the smooth muscle of the stomach and intestines, stimulates the motility of these organs. Confirmation is afforded by the studies of Wolf and Wolf,<sup>15</sup> who, by direct observation on the human stomach, have shown that Prostigmin applied directly to the gastric mucosa will cause vigorous contractions and a fivefold increase in acid output.

Williams<sup>1</sup> in 1941 was the first to suggest the use of Prostigmin for the treatment of heartburn of pregnancy and later Wiley<sup>13</sup> and Roth<sup>14</sup> reported similarly good results in a small series of cases. Mindful of the need for additional confirmatory evidence, it became our plan to conduct a study along similar lines. Because of the strong psychosomatic factor in the production of gastrointestinal symptoms in pregnancy and also because of the multiplicity of successful remedies offered for treatment of this condition, cases were selected by the elimination of those considered not suitable. Accordingly, the subjects reported on in this paper include only women who complained of daily recurrent episodes of heartburn and who failed to obtain relief from a medical regime consisting of increased protein and fat intake; a decreased carbohydrate intake; omission of fatty and fried foods and chocolate from the diet, the elimination of smoking, and the use of aluminum hydroxide in liquid and tablet form. This selectivity eliminated 75 per cent of complainants but practically all were women prior to the twenty-sixth week of their pregnancy, which served to underline the fact

that the symptom is experienced most severely toward the end of pregnancy. All patients, from the time of their first visits, were expressly instructed in the value of proper dietary care during pregnancy and received written instructions detailing proper daily food intake.<sup>16</sup> One c.c. of a 1:2,000 solution (0.5 mg.) of Prostigmin Methylsulfate was injected into the gluteal muscles of patients failing to obtain relief from the medical regime outlined and treatment was judged successful only if followed by the disappearance of heartburn for a period of at least three days. In the great majority of cases with good results there was no return of heartburn for from seven to ten days. Realizing the positive psychic factor in any parenteral injection for a subjective complaint it was decided to adopt a positive approach to the patient, in order, as nearly as possible, to produce the same psychic response to the injection in all patients. Therefore, all women were told at the time of the first injection that they would obtain relief from their heartburn, as "nine out of ten" women did so. To obtain a further control a certain number of women received, without their knowledge, an injection of distilled water, in some, the controls, on their initial injection, and in those who did obtain relief from Prostigmin, at a subsequent injection for the treatment of recurrence.

### Material and Results

A total of 151 patients were included in the study. Of the 136 who received injections of Prostigmin Methylsulfate initially, as outlined above, 124, or approximately 90 per cent, experienced relief lasting for at least three days. The 12 who did not respond were given a second injection, with significant relief in only 2. Forty-eight of the 124 who did respond to the initial treatment required at least one subsequent injection because of recurrence of symptoms. In 4 of this group, the recurrence persisted and it may be significant that all of these were within three weeks of term. By way of controls, each of 15 subjects received an injection of sterile distilled water only 2 reported subjective improvement. In addition, to provide a further check, 15 of the 136 women who had gained relief from an initial injection of Prostigmin were given a second injection consisting only of distilled water. Some "improvement" was reported by 2. The remaining 13 patients of this group, obtaining no relief from distilled water, were then given a second injection of Prostigmin and in all instances they reobtained the relief that they had experienced with the initial injection of Prostigmin.

A possible explanation of the ten initial and four secondary failures in this series is offered by postulating in them the presence of hiatus dilatation and diaphragmatic herniation. Dwyer<sup>17</sup> feels that all esophageal hiatus hernias are congenital in origin and that they can be produced by the increased intra-abdominal pressure caused by the enlarging uterus. Ritvo<sup>18</sup> found the incidence of esophageal herniation to be about 1 per cent in 8,000 routine gastrointestinal series and in half of the cases so demonstrated heartburn was a presenting symptom. The incidence of hiatus hernia in the third trimester of pregnancy is 12.8 per cent.<sup>19</sup> Evans and Bouslog<sup>20</sup> report four intractable cases of heartburn in pregnancy which they ascribed to hiatus hernia and after delivery, with amelioration of symptoms, none could be redemonstrated.

It is interesting to note and difficult to explain why only about 40 per cent of the women required repeated injections of Prostigmin following their initial relief. Of those requiring repeated injections for a return of symptoms, 98 per cent obtained relief. It is probable that heartburn peculiar to pregnancy, in the majority of cases, is capable of undergoing spontaneous remissions and exacerbations and that it is possible that the Prostigmin so "jolts" the lagging intestinal tract as to cause a remission of symptoms for an extended period of time.



At the onset of the study there was some hesitancy about using Prostigmin because of reports in the literature of induced vaginal bleeding in the non-pregnant by the production of a uterine hyperemia<sup>21, 22, 23</sup>; because of the experience of Lubin and Waltman<sup>24</sup> in their attempts to induce abortion with it; because of the attempts of Robins<sup>25</sup> to induce labor with it; and because of the observations of Woodbury and co-workers<sup>26</sup> of an oxytocic effect in the attempted treatment of pre-eclampsia with it. Despite our initial hesitancy, we observed no case in which vaginal bleeding, uterine contractions, induction of labor, or a demonstrable drop in blood pressure followed treatment with Prostigmin.

### Summary and Conclusions

Heartburn peculiar to pregnancy is a neuromuscular phenomenon which may occur at any time throughout gestation. Subject to spontaneous remissions and exacerbations, it is most common and most severe during the last trimester. It is probably due to the hormonal effects incidental to pregnancy on the gastrointestinal tract. It occurs in about two-thirds of all pregnancies, 60 per cent in the first two trimesters and 40 per cent in the last third. Seventy-five per cent can be controlled by a medical regime but practically all such cases have their onset before twenty-six weeks. Prostigmin Methylsulfate 1:2,000 (0.5 mg.) intramuscularly will provide relief for at least three days, and generally from seven to ten days, in 90 per cent of the remaining cases. No adverse effects from doses of this size were noted in this study. Intractable cases may be due to a temporary diaphragmatic herniation due to increased intra-abdominal pressure.

The Prostigmin used in this study was provided by Hoffmann-La Roche, Inc.

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1101 BEACON STREET



## STILLBIRTHS AND NEONATAL MORTALITY OCCURRING WITHIN THE FIRST SEVEN DAYS OF LIFE

### A Review of Forty-Four Autopsied Cases

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**I**N AN attempt to determine if there was some salvage possible in certain stillbirths and neonatal deaths occurring within the first week of life, a review of 5,116 deliveries occurring at St. Elizabeth's Hospital between January, 1946, and July, 1948, was undertaken. In that period of time, there were 5,093 live births and 90 stillbirths. There were 63 sets of twins and 2 sets of triplets.

Seventy-six (1.47 per cent) of the infants born alive died within 48 hours; 26 (0.51 per cent) died after 48 hours, but before one week of life. The total number of babies dying was 102, or 1.9 per cent, of the total liveborn. The stillbirths plus the neonatal deaths within the first seven days of life resulted in a fetal wastage of 192, or 3.7 per cent, of the total births.

Forty-four (22.8 per cent) of these cases were autopsied, and these particular cases are the subject of this paper. An attempt has been made to correlate maternal and fetal factors as well as necropsy findings to see if some salvage was possible. The maternal factors will be reviewed first.

#### Maternal Factors

**Age.**—The average age of the mothers giving birth to live infants was 29.65 years. The youngest was 22 years. There were 25 mothers in this group.

The average age of the mothers giving birth to dead infants was 27 years. There were 19 mothers in this group of whom the youngest was 19 years and the oldest 41.

**Gravidity.**—Fourteen of these patients were primigravidas; 9 secundigravidas; 5 tertigravidas; 8 were in their fourth pregnancy; 2 were in their fifth pregnancy; 1 her sixth pregnancy; and 3 were in their seventh pregnancy. Two infants were delivered at an outside hospital and no history was sent in with the child other than that the mother was Rh negative.

**Prenatal Factors.**—The prenatal course was reviewed with regard to Rh factor, toxemias, ante- or intrapartum bleeding, or any unusual occurrence. There were 20 Rh-positive mothers, 16 Rh-negative mothers, and 8 mothers on whom the Rh factor was not recorded. There were 9 stillbirths and 11 live births in the Rh-positive group. The 16 Rh-negative mothers had 11 live births and 5 stillbirths.

Twelve of the mothers in the Rh-negative group had anti-titers ranging from 1:8 to 1:256. Four of the infants that died were delivered at other hospitals and transferred to St. Elizabeth's Hospital for exchange transfusions.

There were 8 cases of toxemia, of which 5 resulted in live births and 3 in stillbirths.

**Labor and Delivery.**—The average length of labor was 6.5 hours. One was a precipitate delivery. The shortest labor was 45 minutes; the longest 24 hours.

Twenty-two infants were delivered normally; 4 were delivered by means of low forceps; 3 by midforceps; and one by high forceps. There were 5 breech extractions, one version, and 8 cesarean sections.

Medication in these cases varied with the individual physician. In many of the cases no medication was given because of the prematurity of the baby. The actual delivery was accomplished under either oxygen-ether inhalation

anesthesia or spinal anesthesia. Oxygen is employed during labor especially in the late first stage and second stage, with delivery in the early second stage aided by prophylactic episiotomy. No caudal analgesia was employed.

In those cases where medication was given for analgesia, Nembutal and Demerol were the drugs of choice, with scopolamine occasionally being used. These drugs were given in most cases no later than three to six hours before the actual delivery.

One patient did receive more than the average amount of oxytocics. This was an Rh-negative mother with an antititer of 1:16, and an injudicious attempt was made to induce labor by artificial rupture of the membranes and repeated fractional doses of Pitocin. An extraperitoneal cesarean section was finally performed, but the baby was stillborn.

### Fetal Factors

The fetal factors center chiefly around the prematurity or maturity of the infant; whether a fetal heartbeat was heard on admission to the hospital; when the fetal heartbeat was last heard; and, if liveborn, the condition of the baby at birth: whether there was a spontaneous cry, minimal, moderate, or advanced asphyxia or anoxemia, and what attempts were made to resuscitate the baby.

*Prematurity and Maturity.*—There were 28 premature deliveries (one set of twins); 15 full-term deliveries; and one patient was 4 weeks overdue by dates. The average premature infant born was 5.15 weeks from term. One infant was 10 weeks from term; 7 were 8 weeks from term; and the remaining infants varied from one to 7 weeks from term.

The premature infants died from a varying number of causes. The chief cause was erythroblastosis fetalis; congenital alveolar dysplasia was second; atelectasis, pneumonia, and intrauterine asphyxia followed in third place. It will be noticed that in only two cases was prematurity the only anatomical cause discernible at autopsy.

The one case of uric acid infarcts of the kidneys that is reported is rather an unusual one. The mother was a gravida i, Rh positive, with a severe toxemia of pregnancy. She was delivered by low transverse cervical section. The evidence of uremia in this case has led us to a further study of the effect of toxemia on the fetus, and there is some evidence pointing to a rise in the nonprotein nitrogen and uric acid in the fetus that is proportional to the rise of these waste products in the mother. This case, together with the preliminary work that has been done in other cases, is the subject of a separate report now in process.

Atelectasis, occurring in two cases, is a problem for both the pediatrician and the obstetrician. Too often an infant that appears perfectly normal at birth and seems to be well aerated on auscultation will suddenly develop massive collapse of the lungs. House and Owens<sup>1</sup> have written an excellent article on atelectasis of the newborn and have propounded criteria for the determination of atelectasis secondary to bronchial obstruction. The question of bronchoscopy in these cases is discussed, but the problem arises as to how much edema results from the passage of a bronchoscope, no matter how skillfully done.

Congenital alveolar dysplasia occurred in four cases. This condition is still disputed by pathologists, but at St. Elizabeth's Hospital it is felt that it is a definite pathological entity. This interesting condition has been described by MacMahon in two recent articles.<sup>2, 3</sup>

Congenital heart disease accounted for one death.

Finally, the worst offender of all was erythroblastosis fetalis. The disease is of distinct importance in present-day obstetrical care. To date, the only choice we have is exchange transfusion or repeated small transfusions through the scalp veins. Various substances have been tried, among them pertussis vaccine and ethylene disulfonate in an attempt to immunize the fetus.

In the case of the macerated fetuses, the placenta was also examined with no evidence of disease being found.

*Full-Term Infants.*—The causes of death in the full-term infants were chiefly erythroblastosis and intrauterine asphyxia. Atelectasis was present in one case while congenital anomalies of one kind or other accounted for four of the deaths.

The combined causes of death in the 44 infants are summarized in Table I and indicate that erythroblastosis fetalis is the leading cause of infant mortality, followed by intrauterine asphyxia and congenital alveolar dysplasia. Prematurity of itself was responsible for but two deaths. The question now arises as to whether a premature infant born with a stigma of either congenital defects or erythroblastosis can be said to have succumbed because of prematurity. Many of these infants had defects that would not be compatible with life in a full-term infant. That is, was the premature birth an attempt on the part of nature to expel a fetus that was not compatible with existence in the extrauterine world? So little is known of the mechanism or reason for premature births that no workable hypothesis can be put forth.

Five infants in this series receiving exchange transfusions died. Two died two days following the transfusion; one died one day following the transfusion; and two died within four hours. One of the deaths was due apparently to overload of the heart during the transfusion.

TABLE I. COMBINED CAUSES OF DEATH

CAUSE OF DEATH	NUMBER
Erythroblastosis	14
Intrauterine asphyxia	7
Congenital alveolar dysplasia	5
Macerated fetus	4
Atelectasis	3
Anencephalic monster	2
Prematurity	2
Congenital heart disease	2
Pneumonia, aspiration type	2
Osteogenesis imperfecta	1
Encephalocele	1
Uric acid infarcts of kidneys	1
Total	44

Fetal heartbeats were audible in three cases although the infants were still-born. One infant had an occult prolapse of a long cord; one a congenital alveolar dysplasia and absence of the gall bladder; the third was an erythroblastotic.

### Summary

1. Forty-four autopsied stillbirths and neonatal deaths are reviewed.
2. The anatomical features of these cases are reviewed.
3. Rh factor, prenatal course, delivery, analgesia, and anesthesia have been recorded.
4. Erythroblastosis has been found to be the chief cause of death.

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## ALKALINE PHOSPHATASE IN HUMAN ENDOMETRIUM\*

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THERE has been considerable study in recent years of cellular physiology and its relationship not only to normal processes but also to neoplastic disease. It may be that the knowledge of the changes taking place within the individual cell may be a most important link in the discovery of the cause of neoplasia. Therefore, the study of the intracellular enzymes may be most enlightening and this paper deals with the results of a study of one of these enzymes, i.e., alkaline phosphatase.

Atkinson and Gusberg<sup>1</sup> have demonstrated the variations in the amount of alkaline phosphatase in the human endometrium during the phases of the menstrual cycle, hyperplasia, and adenocarcinoma of the endometrium. They found a high level of phosphatase in hyperplasia but an absence in adenocarcinoma.

The present study was undertaken to determine if their findings could be corroborated and also to include decidua and chorionic epithelium. The similarity between embryonic and neoplastic tissues is well known and, if a common metabolic factor could be found, a step forward would be made in determining the cause of malignancy. By including decidua and chorionic epithelium, therefore, it was hoped a similarity might be found between them and malignancy as regards the amount of alkaline phosphatase.

### Method and Material

The determination of the alkaline phosphatase was done by the histochemical method of Gomori.<sup>2</sup> The depth of staining indicated the amount of alkaline phosphatase present, i.e., the darker the stain, the more alkaline phosphatase.

TABLE I. ALKALINE PHOSPHATASE IN HUMAN ENDOMETRIUM

KIND OF TISSUE	CASES GRADED BY AMOUNT OF PHOSPHATASE					TOTAL NUMBER OF CASES
	0	1	2	3	4	
Proliferative endometrium	3	7	0	14	11	35
Secretory endometrium	1	2	1	7	9	20
Premenstrual endometrium	1	10	2	2	0	15
Hyperplasia of endometrium	0	5	1	7	5	18
Adenocarcinoma of endometrium	5	0	0	0	0	5
Decidua	13	1	0	0	0	14
Chorionic epithelium	0	0	0	5	0	5
Endocervix	3	0	0	0	0	3
Squamous epithelium (cervix)	1	0	0	0	0	1
Endometritis	2	0	0	0	0	2
Synectial endometritis	0	0	0	0	1	1
						119

\*Read before the Brooklyn Gynecological Society, Oct. 19, 1949.



There were 119 cases studied in this series, which were divided into eleven categories. (Table I.)

The material was obtained either by curettage or hysterectomy and was fixed immediately after surgical removal. The amount of alkaline phosphatase present in the tissues was graded from 0 to 4 with Grade 4 representing the largest amount of the enzyme. (Table I.)

Fig. 1.

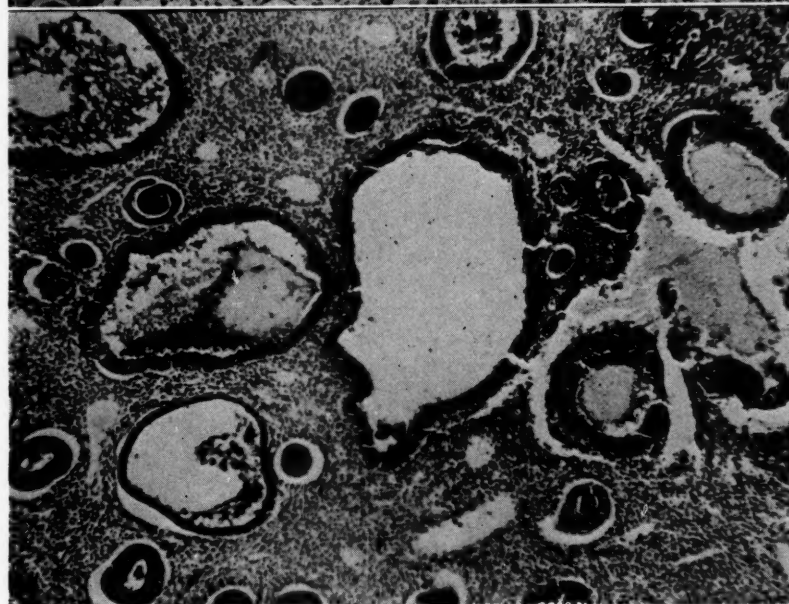
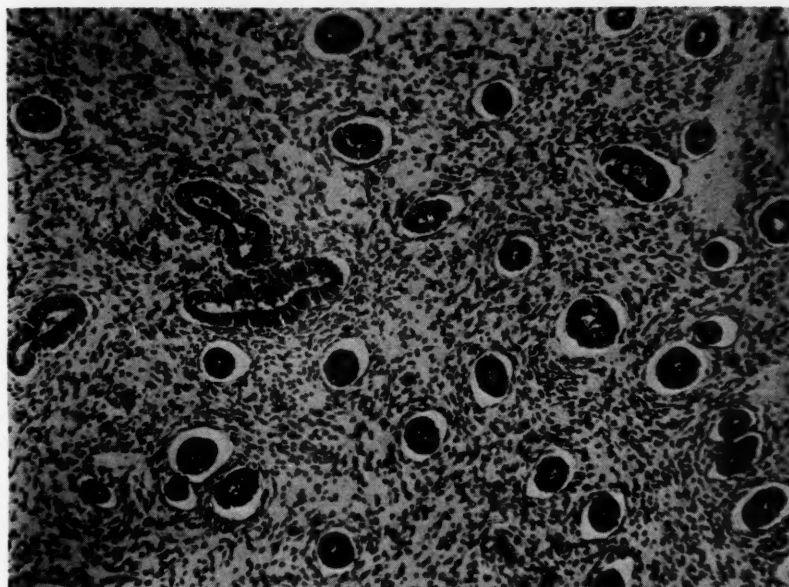


Fig. 2.

Fig. 1.—Proliferative endometrium. Large amount of alkaline phosphatase represented by the dark staining of the epithelium.

Fig. 2.—Hyperplasia of endometrium. Large amount of alkaline phosphatase similar to that shown in Fig. 1.

When alkaline phosphatase was found in the endometrium it was located in the peripheral portion of the epithelial cells, lumina of the glands, and the endothelium of the blood vessels.

Fig. 3.

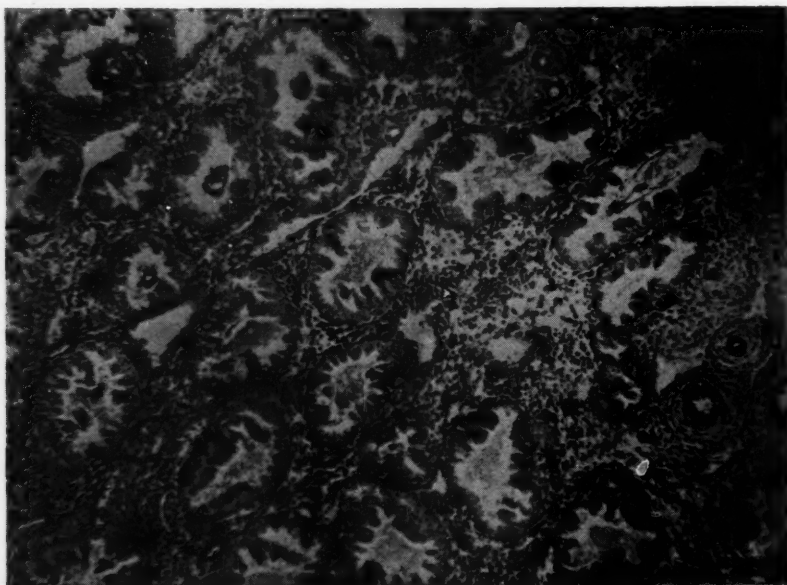


Fig. 4.

Fig. 3.—Adenocarcinoma of endometrium. Absence of alkaline phosphatase except in blood vessels.

Fig. 4.—Decidua. Absence of alkaline phosphatase except in blood vessels.

### Results

The majority of specimens in the proliferative and secretory phases of the menstrual cycle contained a large amount of alkaline phosphatase (71.4 per cent

and 75 per cent, respectively, were in Grades 3 and 4). However, as the menstruating phase was approached, there was a loss of this substance so that 66⅔ per cent of the specimens in the premenstrual phase contained very little or no alkaline phosphatase.

The cases of hyperplasia of the endometrium showed the same findings as those in the proliferative phase of the normal cycle. Sixty-six and two-third per cent of these cases were placed in Grades 3 and 4. On the other hand, the five cases of adenocarcinoma of the endometrium had no alkaline phosphatase.

The study of the tissues of pregnancy revealed an interesting finding. Decidua contained no alkaline phosphatase but the chorionic epithelium had a moderate amount of the enzyme in its cells.

Cervical epithelium, both the endocervix and squamous portion, contained no alkaline phosphatase.

It would appear from the study of the endometrium of the normal menstrual cycle that when the estrogen levels are high but not counteracted by progestin, alkaline phosphatase is usually present in large amounts. However, as the premenstrual phase is entered and both estrogen and progestin are at high levels, alkaline phosphatase disappears. Moreover, in hyperplasia of the endometrium, where usually there is a high estrogen level or a low progestin level, alkaline phosphatase is present in amounts similar to those found in the proliferative phase. It would appear, therefore, that there is a direct relationship between the levels of the female sex hormones and the amount of alkaline phosphatase in the endometrium. Apparently, the ratio between estrogen and progestin is more important than the actual level of estrogen.

The absence of alkaline phosphatase in carcinoma of the endometrium was a constant finding and in direct contrast to hyperplasia. It has been suggested by many authors, including Gusberg<sup>3</sup> that hyperestrogenism produces endometrial hyperplasia and possibly malignancy of the endometrium. Moreover, it is believed by many that hyperplasia is a forerunner of malignancy. If this be true, a marked change in intracellular enzymic activity takes place between the hyperplastic state and the development of the malignancy. The mechanism producing this change may explain the reason for the development of the malignancy but the nature of this mechanism is not known at present. The author is not aware of any studies on the levels of the female sex hormones in cases of carcinoma of the endometrium, but this report would suggest that such a study might be most enlightening.

Another interesting observation from the study was the similarity between decidua and carcinoma of the endometrium. Alkaline phosphatase was absent in both tissues but was present in large amounts in chorionic epithelium. Cancer tests often give false positive results during pregnancy and the above finding may be a partial explanation for this discrepancy.

This study should be considered purely investigative and it is hoped that its results may act as a stimulus to others to delve deeper into the study of intracellular metabolism because the author believes that this type of research will be most important in the advancement of our knowledge of malignancy.

### Summary

1. The amount of alkaline phosphatase was studied in 119 specimens of endometrium.
2. Alkaline phosphatase was present in large amounts in the proliferative phase but low or absent in the premenstrual phase.
3. Alkaline phosphatase was absent in carcinoma of the endometrium but present in large amounts in hyperplasia of the endometrium.

4. Decidua contained no alkaline phosphatase but it was present in chorionic epithelium.

5. The relationship of the female sex hormones to alkaline phosphatase has been discussed.

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429 CLINTON AVENUE



## THE TREATMENT OF GONORRHEA IN WOMEN WITH STREPTOMYCIN\*

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THERE is laboratory and clinical evidence that the gonococcus is sensitive to streptomycin at blood levels ordinarily obtained by the usual dosage schedules.<sup>1-7</sup> The majority of clinical reports have dealt with the successful use of streptomycin in the treatment of gonorrheal urethritis in men. It seemed proper, therefore, to investigate further the efficacy of streptomycin in the treatment of gonorrhea in women.

### Selection of Cases

Twenty-four women patients with gonorrhea were originally included in this study. Critical analysis was ultimately confined to eighteen patients (Table I): Five were omitted because of inadequate follow-up. An additional patient inadvertently received penicillin during the course of streptomycin therapy and also was omitted. Sixteen of the eighteen cases analyzed were classified as acute gonorrheal pelvic inflammatory disease. The remaining two cases were asymptomatic and were discovered by routine cervical smears during a gynecologic examination.

The presence of gram-negative intracellular diplococci in a cervical or urethral smear was in all instances the ultimate criterion for the inclusion of a case in this series.

In addition to urethral and cervical smears, pretreatment sedimentation rates<sup>8</sup> (Cutler) and oral temperatures were obtained.

### Therapy

Seventeen of the patients were treated entirely as outpatients. One was admitted to the hospital. The hospital patient was given 750 mg. of streptomycin intramuscularly daily for six days. The remaining patients received one dose of 750 mg. of streptomycin intramuscularly when the diagnosis of gonorrhea was confirmed. Streptomycin, 750 mg. intramuscularly was then given each day for the next two days.

There was no clinical evidence of streptomycin toxicity.

### Follow-up Regime

While streptomycin was being given, the patients were seen daily. Interval histories, temperatures, gynecological examinations, cervical and urethral smears, and sedimentation rates were repeated each day.

Following treatment, so far as possible, the patients were seen once each week for three weeks, and the same procedures repeated. They were then seen monthly for three months with repetition of the same procedures.

\*Merck & Co., Inc., Rahway, N. J., supplied streptomycin for this study.

TABLE I.

CASE	AGE (YEARS)	RACE		SIGNS AND SYMPTOMS	SEDIMENTATION RATE		TREATMENT	RESULT	
		WHITE	NEGRO		PRE- TREAT- MENT	TERMI- NAL		TIME AFTER TREATMENT SMEARS BE- CAME NEG.	CURED
1	18		X	Present	30	10	750 mg. strepto- mycin daily for 3 days	1 day	Yes
2	18	X		Present	15	12	750 mg. strepto- mycin daily for 3 days	1 day	Yes
3	29		X	Present	18	9	750 mg. strepto- mycin daily for 3 days	1 day	Yes
4	26		X	Present	—	—	750 mg. strepto- mycin daily for 3 days	2 days	Yes
5	21		X	Present	24.5	20	750 mg. strepto- mycin daily for 3 days	2-10 days	Yes
6	21		X	Present	21	16	750 mg. strepto- mycin daily for 3 days	2-10 days	Yes
7	25		X	Present	22	13	750 mg. strepto- mycin daily for 3 days	2 days	Yes
8	23		X	Present	25	16	750 mg. strepto- mycin daily for 3 days	1 day	Yes
9	24		X	Present	25	10	750 mg. strepto- mycin daily for 6 days	2 days	Yes
10	26		X	Present	17	5	750 mg. strepto- mycin daily for 3 days	1 day	Yes
11	15		X	Absent	10	7	750 mg. strepto- mycin daily for 3 days	2-10 days	Yes
12	20		X	Present	28	20	750 mg. strepto- mycin daily for 3 days	2-10 days	Yes
13	20		X	Present	28	26	750 mg. strepto- mycin daily for 3 days	2 days	Yes
14	33		X	Present	23	19	750 mg. strepto- mycin daily for 3 days	2 days	Yes
15	21		X	Present	30	—	750 mg. strepto- mycin daily for 3 days	2-10 days	Yes
16	25		X	Present	22	18	750 mg. strepto- mycin daily for 3 days	1 day	Yes
17	16		X	Absent	24	23	750 mg. strepto- mycin daily for 3 days and repeated 1 week later	Remained positive	No
18	19		X	Present	25	20	750 mg. strepto- mycin daily for 6 days	1 day	Yes

## SUMMARY

NO. OF CASES						AVERAGE SEDIMEN- TATION RATE		TIME AFTER TREAT- MENT THAT SMEARS BECAME NEGATIVE			PER CENT CURED
	RACE		AGE (YEARS)			PRE- TREAT- MENT					
	WHITE	NEGRO	15-19	20-29	30-35			1 DAY	2 DAYS	2-10 DAYS	
18	1	17	5	12	1	22.8	15.3	7	5	5	94

For the purposes of this study, the patients were regarded as cured if there were three consecutive negative smears. The earliest time that a patient could accumulate three consecutive negative smears was at the first weekly examination.

**Clinical Picture Before Treatment**

The majority of patients complained of dysuria, vaginal discharge, and severe lower abdominal pain.

The predominant signs were a temperature elevation of 1 to 4° F., slight to severe lower abdominal and pelvic tenderness, and an inflamed cervix with a purulent discharge.

Positive smears were obtained in all cases. Seven patients had positive cervical smears only, one patient had a positive urethral smear only, and ten had positive urethral and cervical smears.

Nine patients had an adnexal mass ranging in size from 4 to 8 cm. in diameter.

All initial sedimentation rates determined, except one, were elevated, the average being 22.8 mm. in one hour. (Normal = 0 to 10 mm. in one hour.)<sup>8</sup>

**Clinical Picture After Treatment**

Following the institution of therapy, temperatures became normal within forty-eight hours except in three cases, and in these three the temperature was normal at the first weekly examination.

Signs of peritoneal irritation were diminished within twenty-four to forty-eight hours and had disappeared by the end of the first week.

The cervical discharge gradually diminished in all patients during the first week after treatment.

Pelvic tenderness decreased markedly in twenty-four hours following the first injection of streptomycin, and was absent in all patients by the end of the first week following completion of treatment. All adnexal masses, except in one patient, decreased in size following streptomycin therapy. The masses were absent by the end of two months in five of the nine cases. Three of the four patients with persistent adnexal masses still had masses present at the end of three months, but they were distinctly smaller. The fourth, the hospital patient, was not seen after the third-week follow-up. At that time her mass had remained unchanged.

The sedimentation rate dropped in all cases retested. At the end of the follow-up period the average sedimentation rate was 15.3 mm. in one hour, the average decrease being 7.5 mm. in one hour.

In seven cases the cervical and urethral smears became negative within twenty-four hours after the first injection of streptomycin, and remained negative. The smears became negative in five additional cases within forty-eight hours and remained negative. In five more cases the smears became negative between the forty-eighth hour and the first weekly follow-up, and remained negative.

The positive cervical and urethral smears of one patient were not converted by a three-day course of streptomycin. One week later 750 mg. of streptomycin were again given daily over a three-day period. Two weeks later the smears were still positive. Then 300,000 units of penicillin in oil and beeswax were given daily for three days and the cervical and urethral smears became negative.

Perihepatitis apparently developed in one patient one month following a successful course of streptomycin for acute gonococcal pelvic inflammatory disease. Cervical smears had become negative forty-eight hours after beginning treatment. Because of the right upper quadrant symptoms, 750 mg. of streptomycin were given intramuscularly. Marked improvement was noted in twenty-four hours and by the end of forty-eight hours the patient was asymptomatic.

In one patient a *Trichomonas vaginalis* infection was present along with acute gonococcal pelvic inflammatory disease. The gonococcal disease responded to streptomycin. The *Trichomonas* infection was not altered.

### Summary

1. Eighteen women with gonorrhea were treated with streptomycin.
2. Seventeen patients were considered cured.
3. One patient was not cured with two courses of streptomycin.
4. The selection of cases, therapy, follow-up regime, and pre- and post-treatment findings are discussed.

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## **STUDIES ON UTERINE SINUS AND AMNIOTIC FLUID PRESSURES IN THE FULL-TERM PREGNANT UTERUS**

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**I**T SEEMED to us that a knowledge of the pressures in the uterine venous system would not only be of academic interest, but would most likely prove to be of practical value. With this in mind, we undertook a study of the pressures within the uterine sinuses, the intact amniotic sac, and pressure changes occasioned by intrauterine packing.

### **Materials and Methods**

Patients were selected in whom elective cesarean section was to be performed. With the uterus exposed, a transfusion needle of the Unger or Kaliski type was inserted into a uterine sinus. In almost any area punctured, a venous flow was readily obtained. When blood was seen to flow freely, a standard spinal manometer was attached to the needle by means of a 5 inch length of rubber tubing, the manometer and tubing having previously been filled with 2.5 per cent sodium citrate solution. The reading was taken directly from the manometer. For the amniotic sac readings, the manometer system was attached after amniotic fluid began to flow from the needle. When taking the readings, the lower end of the manometer was held on the same level with the point of the needle. Respiratory excursions and variations in uterine tone in some of the patients accounted for the fluctuations noted in the readings. The findings are shown in Table I.

The pressure changes created by gauze packing were measured by means of a water-filled balloon inserted into the uterine cavity and attached to the manometer system.

In ten cases, a comparison was made between the prothrombin time, sugar and urea in the uterine and general circulation, blood being drawn simultaneously from the uterine sinus and the antecubital vein. These determinations were discontinued after we noted that there were no significant differences.

### **Comment**

The physical fact that liquids cannot escape when a greater force is opposed to a leaking portion of a fluid system, leads us to believe that postpartum hemorrhage can be successfully treated by making use of this principle. The highest pressure found by us was 300 mm. of water. In accordance with the previously mentioned physical law, an intrauterine pressure higher than the one in the vessel from which leakage is taking place should cause cessation of bleeding. Higher pressures can be readily obtained by gauze packing or by an intrauterine balloon.

We are aware of the fact that the normal mechanism for the arrest of uterine hemorrhage is compression of blood vessels by the contraction of uterine muscle fibers.<sup>1, 2</sup> However, cessation or retardation of bleeding from an open vessel affords the organism an opportunity to form a clot. When packing is

employed, not only is the effect of pressure obtained, but in addition the physiological benefit of uterine muscle compression is secured because of the irritation and consequent stimulation of the muscle fibers by an intracavity foreign body.

There might possibly arise a question as to whether our readings are actually sinus readings. Some even deny the presence of uterine sinuses.<sup>3</sup> However, the great majority of histologists and embryologists are agreed that the uterine sinus is a proved structure.<sup>4, 5</sup> We noted that in none of our cases did blood spurt from the needle, as one would expect had we entered an artery. In a rather extensive experience with postpartum hemorrhage, we have observed that the blood flow from the uterine cavity is even and nonspurting, except in instances of laceration. We therefore feel that the vessels usually responsible for the hemorrhage are venous in nature.

TABLE I

AGE IN YEARS	PARA	ANESTHESIA	BLOOD PRESSURE	VENOUS PRESSURE (ANTE- CUBITAL) (MM. H <sub>2</sub> O)	UTERINE SINUS PRESSURE (MM. H <sub>2</sub> O)	AMNIOTIC FLUID PRESSURE (MM. H <sub>2</sub> O)
37	0	Spinal	120/90	135	210	150
35	i	Spinal	118/84	220	220	
34	0	Spinal	130/74		190	
33	i	Spinal	125/50		165-172	
34	ii	Nitrous oxide, ether	130/80		130	
38	i	Spinal	135/80		60	60
39	0	Nitrous oxide, ether	100/70	350	230	210
22	0	Spinal	145/90	150	190-230	
28	i	Spinal	100/80		140	
32	i	Spinal	108/65	110	188	
29	0	Spinal	95/50	170	190-205	
29	i	Nitrous oxide, ether	110/80		60	
31	ii	Spinal	150/98	190	160	
20	0	Spinal	110/80	120	170-300	
23	0	Spinal	110/75	140	140-162	
42	0	Spinal	120/80		160	
37	ii	Spinal	125/65		140-180	
34	0	Spinal	130/80		140	290-340
28	i	Nitrous oxide, ether	120/70		230-260	
31	ii	Spinal	114/70		Too low to read	
29	i	Nitrous oxide, ether	120/80		140-160	
35	i	Nitrous oxide, ether	125/75		190-270	
36	0	Spinal	130/82	150	230	180-200
29	i	Nitrous oxide, ether	90/60		230	
31	i	Spinal	120/84	190	210	195
45	0	Spinal	142/100	80-90	120-140	
30	0	Spinal	95/60		120-160	
36	0	Spinal	122/68		Too low to read	
38	ii	Nitrous oxide, ether	120/70	280	210-220	
35	ii	Spinal	80/60		250-300	

Our packing experiment both in vitro and in vivo has convinced us that it is possible to increase the pressure in the uterus above that existing in the venous sinuses and thus control hemorrhage. We packed a uterus that was removed from a patient at the end of the fifth month of gestation with five yards of gauze and the intracavity pressure registered 250 mm. of water. A similar experiment was conducted in a patient at the time of cesarean section. The original intrauterine pressure was found to be 60 mm. of water. After five yards of packing it rose to 120 mm., after ten yards to 170 mm., and after a total of fifteen yards, the pressure reading was 295 mm. of water.

Recently a group of obstetricians have criticized the use of uterine packing as a method of treatment in postpartum hemorrhage. The claim made by this group is that blood flow is controlled solely by muscular compression of the uterine vessels. While we concur in the opinion of Barnes<sup>1</sup> that blood loss is physiologically controlled in the pregnant uterus by muscular contraction, nevertheless, the fact stands out and has been observed by many clinicians<sup>6, 7</sup> that intrauterine packing is an effective measure in the treatment of postpartum hemorrhage. We believe that an effective method of treatment should not be discarded because it achieves results by a mode of action that is not in strict conformity with our present physiological knowledge.

### Summary

The uterine venous sinus pressures were determined in thirty patients. The lowest reading was 60 mm. of water and the highest 300 mm. of water, giving an average of 180 mm. of water.

The pressure in over 60 per cent of our cases was between 150 and 230 mm. of water.

Uterine packing in vitro and in vivo caused significant elevations in intra-uterine pressure.

Pressures in the uterine veins and sinuses can be readily measured.

The application of the principle relating to the action of opposing forces in a fluid system may prove a valuable addition to the treatment of postpartum hemorrhage.

We wish to thank Drs. A. B. Tamis, H. Gordon, and W. LaVine for permitting us to make these determinations in five patients of this series.

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## A STUDY OF THE TRICHOMONAD POPULATION IN EXPERIMENTALLY INFECTED RHESUS MONKEYS\*

### I. The Efficiency of Intensive Microscopic Search Compared to Culture Technique

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IN A recent study, Johnson, Kupferberg, and Hartman<sup>1</sup> have demonstrated radical changes in the numbers of vaginal trichomonads at certain periods in the menstrual cycle of experimentally infected rhesus monkeys. Typically, the population peaks appear three to five days before or after the menstrual flow. During the mid-portion of the cycle, *Trichomonas vaginalis* has been found with difficulty in certain animals and may escape detection in others. It is not known whether these organisms are entirely absent from the mucosal surfaces for short periods, or whether they are present in too few numbers to be detected by the routine microscopic examination of vaginal preparations.

It is the purpose of this paper to report the findings to date on the efficiency of a culture method when trichomonads are not found in an intensive microscopic search of the smear.

#### Method

A colony of nine female rhesus monkeys maintained in separate cages were used in this study. Observations were made over a nine-week period, May 13 to July 15, 1949. Vaginal infections were established, except as noted below, by introducing with a tuberculin syringe 1 ml. of a forty-hour culture of bacteria-free *Trichomonas vaginalis* in Simplified Trypticase Serum medium.<sup>2</sup>

Three vaginal swabbings were taken three times a week from each animal by means of cotton applicators introduced between blades of a nasal speculum. Specula were boiled between examinations to prevent cross-infection. Two applicators were placed into tubes containing 1 ml. of Ringer's solution and slightly agitated to disperse the vaginal discharge. In the case of monkeys found to be negative by microscopic examination, the third swab, not in saline, was planted in STS† medium with penicillin (Merck) 250 u. per milliliter<sup>3</sup> and streptomycin (Merek) 1 mg. per milliliter<sup>4</sup> and incubated at 37° C. for a minimum of ten days. Cultures were examined for trichomonads at 48 hour intervals. When trichomonads were not found on examination of ten low-power fields, an intensive search in 100 high-power fields was made.

#### Results

Two monkeys, No. 2 and No. 8, were refractory to the experimental infection during the nine-week period. Trichomonads were not demonstrated either by the intensive microscopic examination of 100 fields (high-power) or by culture in STS medium. At the end of the nine-week period, the vaginal

\*This paper was submitted in partial fulfillment of course requirements in Parasitology, Graduate School of Arts and Sciences, New York University.

†STS, simple trypticase serum.



tract of both monkeys was flushed thoroughly with 3 c.c. sterile Ringer's solution containing penicillin (Merck) 250 u. per milliliter and streptomycin (Merck) 1 mg. per milliliter. Washings were withdrawn by Asepto syringe and planted into 27 ml. volumes of STS medium containing penicillin and streptomycin and incubated for ten days at 37° C. Cultures were examined at 48 hour intervals but no Protozoa were observed during the incubation period.

Monkey No. 2 has a history of being trichomonad negative for a continuous period of 171 days despite three experimental inoculations.

Monkey No. 8 has been trichomonad positive for 27 months and maintained the infection in spite of repeated therapy. However, the last trichomonad was seen in March, 1949, and she remained negative to three subsequent attempts at reinfection.

Vaginal swabbings from seven infected rhesus monkeys, negative on intensive repeated microscopic examination for trichomonads, were cultured a total of 38 times. On culture, twenty-six, or 68.4 per cent, were positive; twelve, or 31.6 per cent, were negative (Table I). The samples which proved negative on culture were obtained during midcycle or were restricted to two to three days after the menstrual period and before the peak rise in trichomonad population. These data corroborate the findings of Johnson, Kupferberg, and Hartman.<sup>1</sup>

TABLE I. INTENSIVE MICROSCOPIC SEARCH COMPARED TO CULTURE METHOD  
RESULTS, ON CULTURE, OF SAMPLES THAT WERE NEGATIVE ON MICROSCOPICAL EXAMINATION

MONKEYS EXPTL. NO.	NUMBER FIELDS EXAMINED WITH HIGH-POWER	CULTURE METHOD NO. CULTURES	RESULTS	
			POS.	NEG.
No. 7	100	1	1	0
No. 11	100	1	0	1
No. 14	400	4	2	2
No. 17	600	6	4	2
No. 18	1,600	16	10	6
No. 20	600	6	5	1
No. 23	400	4	4	0

### Conclusion

These data show that where vaginal trichomonads were not demonstrable in rhesus monkeys by intensive microscopic search, the culture technique will reveal their presence in the majority of samples.

It is hoped that a similar technique used to demonstrate the infection in women will make for greater accuracy in diagnosis and therapy.

Acknowledgment is made with thanks of the assistance of Mr. P. Russo in the care and maintenance of the experimental animals. I am also indebted to Drs. Garth Johnson, Carl G. Hartman, and Horace W. Stunkard, and Mr. Alfred B. Kupferberg for advice and encouragement with this problem.

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## Special Article

### MATERNITY AND THE BRITISH NATIONAL HEALTH SERVICE\*

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IN 1944 the Royal College of Obstetricians and Gynaecologists published its well-known Report on a National Maternity Service. This was intended to furnish those who were then engaged in the planning of the new Service with the authoritative views of the College. The fundamental argument of this Report was that to secure the maximum safety of mother and child it was essential that between all the elements in the Service, from midwife at one end, through private doctor and public clinic up to hospital at the other end, there must be the closest administrative collaboration. This conviction dominated all informed obstetric opinion in this country. It had grown up during the years when, alongside the high average maternal death rates of between 4 and 5 in every 1,000 pregnant or parturient women, there were scattered throughout the country many examples of large and unselected maternity practices which showed year after year a rate of 1 per 1,000 or less. In every case such practices were those in which there existed a unity of control and direction of midwife, antenatal clinic, health visitor, doctor, consultant, and hospital. In these areas local initiative and enterprise were saving mothers and babies at a time when the maternal rate was maintained at a high level by the low standards which prevailed throughout the country generally. The low rates in these successful practices were being obtained before the advent of sulphonamides brought a remarkable declension in the deaths from puerperal sepsis and thus from 1936 onwards led to the first downward trend in the national maternal death rates.

It was noticeable that these pioneer practices might exhibit considerable differences in their administration. Thus in some centres, such as Croydon, the control of all agencies concerned with maternity was in the hands of the municipal health authority and its medical officer of health. In other areas, as in the case of Guy's Hospital, the control was centred in the teaching hospital, which provided midwives for the domiciliary midwifery, and also was responsible for the staffing of the antenatal clinics. It was clear that the exact nature of the administrative setup was relatively unimportant. What mattered was the unity of control.

The antenatal clinic was a common concern of the team and in a sense it was the pivot of the service. The normal healthy women, who constituted the bulk of cases, fell naturally to the lot of the midwives for their delivery. The emphasis throughout was on health and the dominant role of the midwife meant that labour was allowed to express itself as a physiological act. The disasters attendant on premature attempts at delivery and "failed forceps" were elim-

\*This article has been contributed by James Young, M.D., Director of the Postgraduate Medical School of London, following a request by the Editor of the JOURNAL, in order to acquaint American physicians with certain of the difficulties and shortcomings of the British National Health Service in the field of obstetrics.

We refrain from comment, but, in view of the proposed Federal legislation relative to compulsory health insurance, believe that these opinions from a prominent English teacher should be of interest.

inated. At the clinic the small proportion of women whose pregnancies departed from the normal were brought under expert care and in the great majority of cases were steered safely through to the end. For them, if necessary, the admission to hospital was an easy arrangement made immediately between two members of the one team. There were no administrative gaps often spelling an inevitable break in the continuity of the care and the tragic loss of valuable time and a rapid tilting of the scales against the patient. The preventable deaths that constitute the great bulk of the maternal death rate and that appear in the mortality statistics under such headings as sepsis, puerperal shock, hemorrhage, etc., were virtually expunged from such a service. Its success was signalized by delivery in two, three, four, or even five thousand consecutive cases without a death.

It had long been recognized in Britain that the best maternity service was often at the disposal of the poorest people living in the neighborhood of a teaching hospital with its free service of midwives, doctors, consultants, and institution. It had also long been recognised that a universal provision on this high standard demanded a national scheme incorporating the principles animating such a service.

There has been much criticism directed against the new service in that, by scattering the responsibility for maternity amongst three administrative bodies, it has failed to secure that unitary control that is recognised by all informed opinion as essential for the safety of mother and child, and in the absence of which even the greatest attention to the technical aspects of midwifery must be largely nugatory. The administrative bodies now responsible are: (a) the Local Health Authorities of which there are over 400. These control the domiciliary midwives, the clinics (antenatal, postnatal, and child welfare) and the health visitors. (b) The Regional Hospital Boards, of which there are 19, and the Boards of Governors of teaching hospitals. These boards administer all hospitals, including the maternity hospitals, and the specialists and consultants in their areas. (c) The Executive Councils, which control the general practitioners who enter the maternity service. These three agencies deal in administrative matters directly with the Minister of Health and there is no procedure by which their activities in respect of maternity can be adequately coordinated. In a recent article I (Young, 1950) have described the new situation as "even more confusing than that existing before the Act." It has tended to replace a system which "though unsatisfactory, yet had some fluidity and allowed of the creation by local enterprise of many efficient peripheral services." For in the days before the Act municipal authorities, in addition to administering the midwife and clinic services, often administered as well the local maternity hospital. As we have seen above many local authorities were able to build up maternity services which succeeded because of the unified control thus made possible. Development along these lines, which many regarded as pointing the true way of progress, has now been made difficult.

It has been pointed out that the new arrangements are the antithesis of that intimate and living collaboration which animates the ideal service. Instead we are faced with a distribution of responsibility so grotesque that, if a woman has a general practitioner as well as a midwife, and if, finally, she is sent to hospital, she may find herself enrolled, it may be within a few days or even a few hours, on the records of three different administrative authorities. Meanwhile there is evidence that in some areas the local maternity authorities (administering midwives and clinics) are seeking a liaison on a committee basis with the Regional Board or Board of Governors (hospital authority) and the Executive Councils (administering the general practitioners) to arrive at a working agreement. It would seem to be clear that the creation of a sound system must centre round the local maternity author-



ities. They administer the 400-odd peripheral services, which must each be built up into a self-sufficing unit, before they can adequately contribute their share to the National scheme. The success with which each such peripheral service can by local negotiation meet its appropriate needs in regard to hospital, consultant, and doctor must determine the final success of the National Service. But collaboration which, under existing conditions, cannot go much further than a loose and friendly accommodation between the three agencies, must inevitably fall short of that compact administrative fusion of interests which is essential for unitary control.

A further criticism has been directed against the new arrangements in respect of general practitioners. It is argued that these may seriously affect the status of the midwife. It is necessary for American readers to recognize the important place which the midwife occupies in British midwifery. During recent decades her training and status have improved and she has assumed more and more the responsibility for the care of the normal case. In 1946, as was shown in *Maternity in Great Britain* (1948), the midwife was personally responsible for 72 per cent of all deliveries including domiciliary and institutional cases. The new Act clearly aims at retaining the midwife in her present position but this is becoming difficult under the scheme which gives the general practitioner a new statutory position. For an inclusive fee a general practitioner providing maternity services undertakes to carry out two antenatal and one postnatal examination and to provide any attendance additional to this, including attendance at labour, which he considers necessary. His remuneration is not increased by additional services. It has been found that to give him a position which leaves to him the decision whether he should or should not be present at the delivery may easily be transformed into a position in which the patient would expect or even demand his presence. If this were to occur in more than a minor degree it would strike a severe blow at the midwife's status and, eventually, at the whole structure of the Service. There are those who believe that these developments have interfered with a healthy trend which had been steadily growing during recent decades by which general practitioners have withdrawn from obstetrics as the midwife has increased her field of work. This trend has been specially evident in some of the larger towns.

To appreciate the nature of some of the other problems which it was hoped the National Health Service would succeed in solving the reader must realise the conditions under which midwifery was carried out generally throughout the country before the operation of the new Act. A comprehensive investigation of these conditions was carried out in 1946 by a Joint Committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee and was financed by the Nuffield Foundation. This Joint Committee, of which I was Chairman, based its study upon a census of all women in England, Wales, and Scotland, totalling about 14,000, who gave birth to a child during one week in March, 1946. With the help of the medical officers of health of 424 maternity and child welfare authorities the circumstances surrounding maternity—the standard and adequacy of antenatal care, care during and after labour, the place and person responsible for this care, the extent of the provision for analgesia, etc.—were all investigated. The investigation provided for the first time information on all these questions and it took special note of the standard and adequacy of the services in relation to the social and economic status of the women.

This study showed that at that time 46 per cent of women were delivered at home and 54 per cent in an institution (hospital or nursing home). It showed that there were great differences in the relative proportion of domiciliary



and institutional delivery according to occupational group. Thus whilst 55 per cent of wives of "agricultural workers," 50 per cent of wives of "manual workers," and 37.6 per cent of wives of "black-coated wage-earners" were confined at home, only 24 per cent of the wives of "professional and salaried workers" were so confined. Similarly steep social gradients were found in some of the other essential services. Thus, whilst 61.4 per cent of wives of professional and salaried workers came under antenatal care during the first trimester this early supervision obtained in only 33.3 per cent of the wives of agricultural workers. The availability of analgesia in domiciliary confinement varied in the same way; it was provided for 57.8 per cent of the wives of professional and salaried workers and for only 18.5 per cent of wives of manual workers.

The investigation of the Joint Committee revealed in a convincing manner the degree in which social and economic status determined the standard of service. This related to the child as well as to the mother. Thus it was found that, after eliminating differences of birth order, the stillbirth rate for the professional and salaried workers (19.1 per 1,000 total births) was significantly lower than that for the manual workers (24.3, difference  $5.2 \pm 0.9$ ). The neonatal death rates for these two groups were respectively 21.7 and 27.8 (difference  $6.1 \pm 0.9$ ). These findings confirmed the evidence of previous studies.

Whilst much of the disadvantage suffered by the lower social orders in respect of the efficiency of the service to which they have access can be eliminated by a national scheme available to all, irrespective of class, this is not universally true. Thus, in some important respects, e.g., in regard to prematurity, stillbirth, and neonatal mortality, this disadvantage might arise not alone from the standard of the obstetric care but, also, from the defective nutrition from which the lower economic classes were apt to suffer. In regard to stillbirth the most noteworthy fact has been the rapid fall from round about 40 per 1,000 total births in the pre-war years to 23 in 1949. This has, with some reason, been ascribed to the general rise in the nutritional levels that during and since the War has resulted from the policy of full employment, of general rationing, and of food priorities extended to pregnant women.

In one respect the new service should succeed in raising the general standards. This relates to the medical personnel serving on the municipal clinics. These clinics date from the time of the Maternity and Child Welfare Act (1918) which laid on local health authorities the statutory obligation of setting up in their areas clinics for antenatal care and for the supervision of children up to the school age. In some instances the medical officers responsible for antenatal care have been doctors engaged in obstetric practice, but in the majority of instances they have been officers who, after some minor training in obstetrics and in child welfare, have acted at the clinics in this dual capacity, with the result that in the course of years they have become more and more out of touch with the realities of obstetrics especially in relation to labour. It has often been argued that in this circumstance we have an explanation of the fact that, despite the large extension of these statutory arrangements for antenatal supervision, there was no appreciable improvement in the maternal mortality rates between 1918 and 1936. The new Service seeks to improve the standard of the work of the clinic by separating the functions of maternity and child welfare and ensuring that those responsible for the antenatal care will be specially trained in and will maintain a continuing contact with practical obstetrics.

### References

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# Department of Reviews and Abstracts

## Selected Abstracts

### Anesthesia, Analgesia

**McNeal, Alice:** The Problems for the Anesthetist When Extreme Relaxation Is Needed for the Patient With Toxemia of Pregnancy, *Anesthesiology* 11: 96, 1950.

The author reports two cases in which death occurred on the delivery table; both of these patients had moderately severe toxemia of pregnancy, and general anesthesia was employed. In these cases ether was used because of the depth of anesthesia required to relax the uterus. Ether may have untoward effects with damage to liver and kidneys; but such ill effects are more likely to become manifest in the postoperative period, and do not explain the sudden deaths in these cases. In the first case ether was given by the open-drop method, but this method provides a minimal amount of oxygen and may have increased the anoxia, especially as there was evidence of some pulmonary edema. In the second case a high oxygen mixture was used and a good airway assured, but this did not prevent the fatality. The intrauterine manipulations employed for delivery (podalic version and extraction) may have produced reflexes that tended to induce circulatory failure; the anesthesia may not have been deep enough to give sufficient relaxation of the uterus. In the toxemia of pregnancy, there is profound disturbance of the peripheral circulation, and the patient is in danger of circulatory failure, even though the blood pressure is high. Anesthesia in the toxemic patient should not be carried to the third plane of the third stage, but this may be unavoidable. Ether vaporized by oxygen and administered through a good airway appears to be the best method. Spinal or caudal anesthesia would not be safe, because of the danger of circulatory failure.

HARVEY B. MATTHEWS

### Cancer, Malignancies

**Kahanpää, V., and Gylling, T.:** Experience With Radiotherapy in Primary Carcinoma of Vagina, *Ann. chir. & gynaec. Fenniae* 38: 164, 1949.

Thirty-three patients with primary carcinoma of the vagina were observed at the Central Institute for Radiotherapy of Helsinki University from 1937 to 1942. Nine cases were unsuitable for even palliative radiotherapy. Twenty-four patients were treated, twelve of whom were free from recurrence five years later.

Therapy consisted of three or four weekly vaginal applications of radium plaques to the entire carcinomatous area, delivering an average total dose of 4,915 mg. hr. Most of the patients received supplementary deep x-ray therapy averaging 4,650 r. There was no primary mortality. Postirradiation sequelae were two rectovaginal fistulas and one small rectal stricture.

DOUGLAS M. HAYNES

### Cesarean Section

**King, Earl B.:** Cesarean Section Experience at the University of California Hospital, *California Med.* 71: 106, 1949.

The author reviews 746 cesarean sections performed at the University of California Hospital from 1907 through 1948, and shows an over-all cesarean section incidence of 3.91

per cent. The maternal mortality rate associated with these cesarean sections has been 1.61 per cent. There has been a steady decline in mortality over the forty-year period and there have been no deaths from cesarean section in the last ten years. The over-all incidence of morbidity associated with cesarean section has been 40.5 per cent and again there has been a significant improvement in recent years. The fetal mortality associated with cesarean section has been 6.1 per cent. In view of recent experience, standards based on figures collected twenty years ago are no longer tenable.

JAMES P. MARR

### Endometriosis

**DeSanto, Dominic A., and McBirnie, John E.: Endometriosis. A Clinical and Pathological Study of 219 Cases, California Med. 71: 274, 1949.**

From the Mercy Hospital, San Diego, Calif., the authors present a clinical and pathological study of 219 patients who presented case-history evidence of endometriosis.

One hundred twenty-four cases of external endometriosis and 95 cases of adenomyosis were analyzed. The two are clinically different diseases which have one feature in common—a reactive fibrosis to aberrant endometrial tissue. They are coexistent in about the same frequency as would result from a noncausal relationship.

The origin of external endometriosis from the epithelial “inclusion” cyst is considered proved histologically. This is the source of origin of most external endometriosis, although occasional involvement from regurgitated endometrium probably occurs. Both the endometrial and the serous cysts have a common parentage in this anlage.

Certain histological features that are considered pathognomonic of endometriosis are: (1) the minimal lesion, (2) the characteristic cuboidal lined cyst, (3) the siderophagic cyst without lining, and (4) the siderophagic nest.

Recognition of the siderophagic nest will permit identification of extinct endometriosis and thus aid in studies to determine the spontaneous or therapeutically induced regression of the disease.

The ability of ectopic deposits of endometrium to become malignant on rare occasions would appear to be proved, but it is a rare occurrence and there is no justification for regarding endometriosis as a premalignant disease.

JAMES P. MARR

### Miscellaneous

**Sandweiss, David J.: The Beneficial Effect of Pregnancy on Human Peptic Ulcer and the Beneficial Anti Ulcer Effect of the Pituitary Adrenal Complex on Experimental Ulcers. A Possible Explanation, Harper Hosp. Bull., p. 228, May-June, 1949.**

The beneficial effect of pregnancy in rheumatoid arthritis and peptic ulcer is related through the pituitary adrenal complex as described by Hench and the author. Investigation of hormones producing this protection included sex steroid principles and chorionic gonadotropin. Leiby, deBoissezon, Esiaschwili, and Payrot are quoted as showing that chorionic gonadotropin stimulates the adrenals. Blumenthal is quoted as having demonstrated in adrenalectomized rats that extracts of human normal pregnant and nonpregnant urine contain adrenocortical activity (Authelone), anti ulcer factor. Other authors are quoted, strengthening the thesis that adrenal stimulation is the benefiting factor.

Three explanations for the beneficial effect of pregnancy and authelone on human peptic ulcer are postulated:

1. The pituitary during pregnancy and possibly during active female sex life stimulates the adrenal cortex. One of the resulting steroids (compound E) may have a beneficial effect on peptic ulcer as on rheumatoid arthritis, and may well be the factor responsible for the improvement of these conditions during pregnancy.

2. Anterior-pituitary-like substance (Antuitrin-S.) has a beneficial effect on experimental Mann-Williamson ulcers. Considerable evidence is quoted, indicating that Antuitrin-S. through its effect on the adrenals is responsible for the improvement.

3. The beneficial effect of parentally administered human nonpregnant female urine extracts may be due to pituitary ACTH or a similar adrenocortical stimulating factor possibly present in the urine of nonpregnant women, which contains little if any A.P.L. The stimulated adrenal cortex produces steroids that could beneficially affect experimental ulcers.

If the beneficial effect of pregnancy on human peptic ulcer is of the same order as that on rheumatoid arthritis it is reasonable to assume that the anterior pituitary adrenocortical complex ACTH and/or compound E is responsible in both. By the same reasoning anti ulcer (Authelone) might be investigated as to its effect on rheumatoid arthritis.

C. J. EHRENBURG

### Newborn

**Hudson, F. P., McCandless, Anne, and O'Malley, A. G.: Sciatic Paralysis in Newborn Infants, Brit. M. J. 1: 223, 1950.**

The authors describe twenty cases of unilateral sciatic paralysis accompanied by gangrene of the buttock on the affected side in six instances. The paralysis was noted usually within the first twenty-four hours of life and in the majority some degree of foot-drop and retardation of growth has been observed. Late appearance is similar to deformities resulting from poliomyelitis. The infants with gangrene of the buttock were noticed to have a bruised appearance shortly after delivery. Later a black slough separated, leaving a clean deep ulcer which finally healed with a scar formation.

The cases all occurred in two Liverpool hospitals between April, 1945, and June, 1948. In all instances the pregnancy and labor were uncomplicated but all infants were in a state of asphyxia and in nineteen instances it is recorded that they were given an injection of Cycliton (diethylamide of 3:5 dimethyliso-oxazol-4-carboxylic acid) (0.05 to 0.5 ml.) in one of the umbilical vessels, supposedly the vein, but probably in one of the umbilical arteries.

The authors state that the blood supply in the fetus to the lower limb is carried by the sciatic artery, the main branch of the internal iliac. It is assumed that the injected medication passed through the hypogastric artery to the internal iliac and sciatic arteries. It is assumed that arterial spasm followed by thrombosis occurred. Animal experimentation did not support this theory.

R. GORDON DOUGLAS

**Abel, Stuart, and Van Dellen, Theodore R.: Congenital Defects Following Maternal Rubella, J. A. M. A. 140: 1210, 1949.**

In 82 letters received in response to a questionnaire, information regarding 84 infants whose mothers had rubella during pregnancy was received (including two sets of twins). Three of these children were stillborn; the mothers of these children had had rubella during the first trimester of pregnancy. Of the 81 living children, 25 are normal, and 56 abnormal. Of the 56 abnormal children, 36 have only one defect and 20 have multiple defects; in 18 of these 20 cases, the mother had rubella in the first trimester of pregnancy. The defects described are congenital heart disease (in 19 cases), congenital cataracts (17 cases), congenital deafness (14 cases), mental deficiency (7 cases), and malformed teeth (5 cases). In 3 cases, the stage of pregnancy during which rubella occurred was not definitely determined; all 3 children showed some abnormality. In the 54 cases in which rubella was known to have occurred in the first trimester of pregnancy, 87 per cent of the infants showed some abnormality; in the 19 cases in which rubella was known to have occurred in the second trimester of pregnancy, 42 per cent of the infants were abnormal; in the 8



cases in which rubella was known to have occurred in the third trimester, only one infant showed an abnormality—cerebral palsy—and this was not considered to be due to the mother's illness. These findings are in general agreement with other reports as to the high incidence of congenital abnormalities in children of women who had rubella during the first trimester of pregnancy. This raises the question of the desirability of therapeutic abortion if an attack of rubella occurs in the first trimester of pregnancy. No definite decision can be reached before additional critical studies are made.

HARVEY B. MATTHEWS

**Landau, Daniel B., Goodrich, Howard R., Francka, W. F., and Burns, Francis R.:** Death of Cesarean Infants: A Theory as to Its Cause and a Method of Prevention, *J. Pediat.* 36: 421, 1950.

The high fetal mortality of babies delivered by cesarean section led the authors to review the literature and record the experience of other workers and to report a technique of their own. They note that Bloxson is of the opinion that a test of labor would decrease the incidence of postsection asphyxia by 25 per cent and that failure to condition the infant by uterine contractions or passage through the birth canal is responsible for many cases of asphyxia.

They also quote the figures of Gellis, White, and Pfeffer, who introduced the procedure of gastric suction to prevent the syndrome of delayed respiratory difficulty.

The authors quote the results of routine intratracheal catheterization as reported by Russ and Strong, whereby they reduced their infant mortality from 8.7 per cent to 1.8 per cent in their series of 137 cesarean babies.

It occurred to the authors that part of the cesarean infant's difficulty might be explained by the deprivation of a considerable amount of the blood, due to the rapidity of tying off the cord, which the baby when delivered by the vaginal route would receive (95 to 107 c.c.).

If the blood deprivation is beyond a critical point, symptoms of secondary or delayed shock may appear two to four hours later, consisting of grunting shallow respirations, air hunger, cyanosis, costal retraction, and terminal convulsions. These the authors maintain, are similar to those observed in the older child or adult in shock from blood loss.

As a consequence in the last 87 cesarean sections, the cord was not clamped until it had collapsed, which occurred in from six to ten minutes. The placenta was delivered, wrapped in a warm towel, and suspended until the cord ceased pulsating.

Since the institution of this technique, only two babies have died following a cesarean section. One death was due to atelectasis on the fourth day and the other was thought due to prematurity and the mother's toxic condition from advanced tuberculosis.

JAMES P. MARR

**Steven, E. M.:** Pure Anti-E Antibody in the Serum of an Rh-Positive Woman, *Lancet*, p. 447, March 11, 1950.

The author records the eighth published case of hemolytic disease of the newborn in which maternal agglutinins were unmixed, and of anti-E nature. The mother was group B, CDe/cde; the father was group A, cDE/cde, a living sibling was group B, CDe/cDE, and the affected infant was group O, CDe/cDE. Since both parents were Rh-positive, maternal serum titers were not investigated antenatally. The infant appeared normal at birth, but developed icterus and a positive Coombs' test within forty-eight hours, and died in four days. Maternal serum studies revealed blocking antibodies for E agglutinin, in titer of 1:16.

IRVING L. FRANK

**Parker, George F.: The Incidence of Mongoloid Imbecility in the Newborn Infant, J. Pediat. 36: 493, 1950.**

In order to throw more light on the exact incidence of mongolism and to determine whether or not the high figure reported by Beidleman pertains to other sections of the country and to other races and economic strata, the author has studied the incidence of the condition in the obstetrical nurseries of the Gallinger Municipal Hospital, Washington, D. C.

During a ten-year period, there were 32 mongoloid imbeciles among 27,931 liveborn infants, an incidence of 1.15 per thousand, or a ratio of one mongoloid imbecile to 873 liveborn infants. There was no significant difference in incidence according to race or the sex of the infant. There was, however, a marked increase in the frequency among prematurely born infants (1:354) as compared to infants born at term (1:1,108).

JAMES P. MARR

### Pregnancy, Complications

**Smale, Leroy E., and Birsner, J. W.: Maternal Deaths From Coccidioidomycosis, J. A. M. A. 140: 1152, 1949.**

In Bakersfield, Calif., in an area where coccidioidomycosis is endemic, 4 deaths due to disseminated coccidioidomycosis occurred in pregnant women, 3 of whom showed symptoms of coccidioidal meningitis. A fifth patient, also with symptoms of coccidioidal meningitis, is still under observation, after delivery of an apparently normal infant. In this patient, examination of the placenta showed no evidence of coccidioidal granuloma. In the other 4 cases there was no evidence of coccidioidal involvement of the genital tract. On the basis of these findings, the authors advise that in all areas where coccidioidomycosis is endemic, all pregnant patients with upper respiratory tract symptoms should be given skin tests and should be carefully watched for signs of dissemination of the disease.

Pregnant patients with symptoms of meningeal involvement should also be carefully studied as to the possibility of coccidioidal infection. While disseminated coccidioidomycosis may be a cause of death in pregnancy, no evidence has been found that this infection can be transmitted to the fetus in utero.

HARVEY B. MATTHEWS

**Stone, Eugene T. Rush: Pregnancy and Internal Carotid Aneurysm, Woman's M. J., Oct., 1949.**

This report from the Department of Gynecology and Obstetrics, Pottstown Hospital, Pottstown, Pa., is unusual. The author maintains that he was unable to find a record of the coexistence of pregnancy and ruptured aneurysm of the internal carotid artery. The patient survived a cesarean section, and later a successful operation for removal of an aneurysm of the right internal carotid artery.

The patient's chief complaints were severe headache, described as "bursting" in type, blurred vision, nausea and vomiting. Positive findings were a blood pressure of only 110/60, a slow pulse, a few granular casts in a urine specimen, slight ptosis of the right upper eyelid, slight dilatation of the right pupil but with reaction to light. An ophthalmologist on two occasions noted only eye-ground changes compatible with a toxemia of pregnancy. However, a neurologist made the correct diagnosis and advocated a surgical operation.

The author states that the appearance of headache and visual disturbances in the course of pregnancy may be due to intracranial aneurysm. An ophthalmologic examination with neurologic consultation should provide an accurate diagnosis and exclude an erroneous diagnosis of toxemia of pregnancy.

He suggests that intracranial aneurysm should be added to the differential diagnosis of toxemia of pregnancy.

JAMES P. MARR

### **Sterility, Contraception, Fertility**

**Guttmacher, Alan F., Tietze, Christopher, and Rubin, Samuel: Contraception Among Two Thousand Private Obstetric Patients, J. A. M. A. 140: 1265, 1949.**

In a study of 2,000 private obstetric patients, it was found that in almost two-thirds of the cases pregnancy occurred after contraceptives had been discontinued for the purpose of initiating pregnancy. In about one-sixth of the cases, contraceptives had never been used. Thus there was a failure of contraceptive methods in only 19 per cent of these cases. The condom and the diaphragm were the two contraceptive methods most frequently employed, and the effectiveness of these two methods was approximately the same. Nine-tenths of the planned pregnancies occurred within a year after contraceptive methods were discontinued, three-fifths within three months. These findings indicate that sterility in a couple desiring children should receive attention after a year, instead of after two or three years.

HARVEY B. MATTHEWS

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## **Items**

### **American Board of Obstetrics and Gynecology**

The annual meeting of the Board was held in Atlantic City, N. J., from May 21 to 27, inclusive, 1950, at which time 259 candidates were certified.

New Bulletins, incorporating changes made at the recent meeting, are now ready for distribution. These changes include adoption of a special form to be designated as the "Appraisal of Incomplete Training Form" which will be forwarded to prospective applicants upon request. Numerous changes concerning graduate training in obstetrics and/or gynecology have also been adopted and will be of special interest to hospitals conducting residency programs as well as to prospective applicants to this Board.

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 2, 1951. Application may be made until Nov. 5, 1950. Application forms and Bulletins are sent upon request made to

PAUL TITUS, M.D., Secretary  
American Board of Obstetrics and Gynecology  
1015 Highland Building  
Pittsburgh 6, Pa.

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### **Award for Research in the Field of Infertility**

The American Society for the Study of Sterility offers an annual award of \$1,000, known as the Ortho Award, for an outstanding contribution to the subject of infertility and sterility. Competition is open to those in clinical practice as well as to individuals whose work is restricted to research in the basic sciences. Essays submitted for the 1951 contest must be received not later than March 1, 1951. The Prize Essay will appear on the program of the 1951 meeting of the Society. For full particulars, address The American Society for the Study of Sterility, 20 Magnolia Terrace, Springfield, Mass.

## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Frederick C. Irving. *Secretary*, Norman F. Miller, 1313 East Ann St., Ann Arbor, Mich. Annual meeting, May 7, 8, 9, 1951, New York City.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, Samuel A. Cosgrove, Jersey City, N. J. *Secretary*, L. A. Calkins, University of Kansas Medical Center, Kansas City 3, Kansas. Annual meeting Hot Springs, Va., September 7, 8, 9, 1950.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Lawrence M. Randall, Rochester, Minn. *Secretary-Treasurer*, John I. Brewer, 24 West Ohio St., Chicago 10, Ill. Annual meeting to be held Thursday, Friday, and Saturday, Sept. 21, 22, and 23, 1950, at the Hotel Schroeder, Milwaukee, Wis.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, Lester A. Wilson, Charleston, S. C. *Secretary-Treasurer*, John C. Burwell, Jr., 416 Jefferson Bldg., Greensboro, N. C. Annual meeting, Ormond Beach Hotel, Ormond Beach, Florida, Feb. 8, 9, and 10, 1951.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, James R. Blos, Huntington, W. Va. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June 19-26, 1950, San Francisco, Calif.
- New York Obstetrical Society.** (1863) *President*, R. Gordon Douglas. *Secretary*, Charles M. McLane, 33 East 68th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Newlin F. Paxson. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Eugene A. Edwards. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, William T. Daily. *Secretary*, J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Houston S. Everett. *Secretary-Treasurer*, W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Edward Friedman. *Secretary*, Robert R. Pierce, 116 William Howard Taft Road, Cincinnati 19, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, Eugene A. Conti. *Secretary*, David Katz, 130—7 Avenue, Pittsburgh 22, Pa. Meetings, first Monday of each month, October to May.
- Obstetrical Society of Boston.** (1861) *President*, Roy J. Heffernan. *Secretary*, Francis Rouillard, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Philip H. Arnot. *Secretary-Treasurer*, R. Glenn Craig, 490 Post St., San Francisco, Calif.
- Washington Gynecological Society.** (1933) *President*, George Nordlinger. *Secretary*, Stafford W. Hawken, 1150 Connecticut Ave., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.



- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Conrad G. Collins. *Secretary*, E. W. Nelson, 1407 S. Carrollton Ave., New Orleans, La. Meetings held October, November, January, March, and May.
- St. Louis Gynecological Society.** (1924) *President*, Matthew W. Weis. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo., Regular meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Donald Dallas. *Secretary*, Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Julius McIver, Dallas. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex. Annual meeting, Dallas, Texas, September, 1949.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, O. W. Picard. *Secretary*, Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Gynecologists and Obstetricians.** (1938) *President*, Nathan N. Cohen. *Secretary*, Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** (1939) *President*, M. Y. Dabney. *Secretary*, Buford Word, 929 South Twentieth St., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Charles D. Kimball. *Secretary-Treasurer*, Robert K. Plant, 732 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.
- Denver Gynecological and Obstetrical Society.** (1942) *President*, Edward L. Harvey. *Secretary-Treasurer*, Jack M. Simmons, Jr., 804 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, J. W. Prentice. *Secretary-Treasurer*, Alice D. Watts, 324 East Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, D. Dalton Deeds. *Secretary*, Jesse A. Rust, Jr., 3115 University Ave., San Diego 4, Calif. Meetings held on the last Friday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, H. A. Wheeler, Grand Forks. *Secretary*, C. B. Darner, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Richard B. Nicholls. *Secretary*, Chester D. Bradley, 2914 West Avenue, Newport News, Va.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Wayne Brehm. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Robert S. Millen. *Secretary-Treasurer*, Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Charles W. Frank. *Secretary*, Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Richard B. Schutz. *Secretary*, William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, A. M. McCausland. *Secretary-Treasurer*, Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, H. B. Atlee. *Secretary*, K. M. Grant. Annual meeting, June, 1950.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, H. H. Gibson. *Secretary-Treasurer*, E. A. Riemenschneider, Second National Bldg., Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio Bldg.
- Minnesota Obstetrical and Gynecological Society.** *President*, Russell J. Moe. *Secretary*, John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.

- Miami Obstetrical and Gynecological Society.** (1946) *President*, Homer L. Pearson. *Secretary*, John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Ralph Luikhart. *Secretary-Treasurer*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, John W. Records. *Secretary-Treasurer*, Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, J. L. Reycraft. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, George B. German. *Secretary*, C. Norman Witte, Pt. Pleasant, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, K. S. Tom. *Secretary*, S. Nishijima, 1221 Victoria St., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists.** *President*, Gerald Kinzel. *Secretary-Treasurer*, Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, Albert Hirsheimer. *Secretary*, Walter K. Gregg, Dayton, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.
- Queens Gynecological Society.** (1948) *President*, Edward C. Veprovsky. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.
- Mississippi Association of Obstetricians and Gynecologists.** (1947) *President*, R. A. Street, Jr. *Secretary*, William Weiner, Barnett-Madden Bldg., Jackson, Miss. Meetings held semiannually.
- Florida Obstetric and Gynecologic Society.** (1948) *President*, Robert G. Spicer. *Secretary-Treasurer*, Dorothy D. Brame, 1235 Kuhl Ave., Orlando, Fla. Next annual meeting, April, 1951, at Hollywood, Fla.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, J. Dechard Guess. *Secretary*, Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, W. Herbert Burwig. *Secretary*, Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.
- El Paso Gynecological Society.** (1948) *President*, Gerald H. Jordan. *Secretary-Treasurer*, Gray E. Carpenter, 303 N. Oregon St., El Paso, Texas.
- Kentucky Obstetrical and Gynecological Society.** (1947) *President*, A. J. Whitehouse. *Secretary*, Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.
- Indianapolis Obstetrical and Gynecological Society.** (1947) *President*, David L. Smith. *Secretary*, Sprague H. Gardiner, 314 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.
- Houston Obstetrical and Gynecological Society.** (1939) *President*, John A. Wall. *Secretary-Treasurer*, Herman L. Gardner, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.
- Iowa Obstetric and Gynecologic Society.** *President*, J. H. Randall. *Secretary*, William C. Keettel, Iowa City, Iowa.
- Memphis Obstetrical and Gynecological Society.** (1950) *President*, James M. Brockman. *Secretary*, James H. Smith, 1195 Poplar Ave., Memphis 5, Tenn. Meetings, fourth Friday, October to May.
- Birmingham Obstetrical and Gynecological Society.** (1949) *President*, W. N. Jones. *Secretary*, Herbert H. Thomas, 1005 South Twenty-First St., Birmingham, Ala. Meetings four times yearly.
- Mobile Obstetrical and Gynecological Society.** (1949) *Secretary*, O. M. Otts, 1059 Dauphin Street, Mobile, Ala.